The mechanisms of change and implementation of cognitive behaviour therapy for chronic fatigue syndrome

Jan-Frederic Wiborg

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Jan-Frederic Wiborg

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Promotoren:	prof. dr. G. Bleijenberg
	prof. dr. M.J.P. Wensing
Copromotor:	dr. H. Knoop
Manuscriptcommissie:	prof. dr. A.E.M. Speckens, voorzitter
	prof. dr. B.G.M. van Engelen
	prof. dr. S. Visser, Universiteit van Amsterdam
Paranimfen:	Marianne Heins
	dr. Ivo Rieu

In memoriam…

Ingrid Elli Wiborg
(April 1950 - Juni 1986)

There is nothing more practical than a good theory.

Kurt Lewin

Contents

1

General Introduction

Cognitive behaviour therapy (CBT) is an evidence-based intervention for patients who suffer from chronic fatigue syndrome (CFS). The six empirical studies which are presented in this thesis seek to answer the questions *why* CBT for CFS works and how it can be successfully implemented outside specialised treatment settings. This first chapter gives a general introduction to the topic and an outline of the thesis.

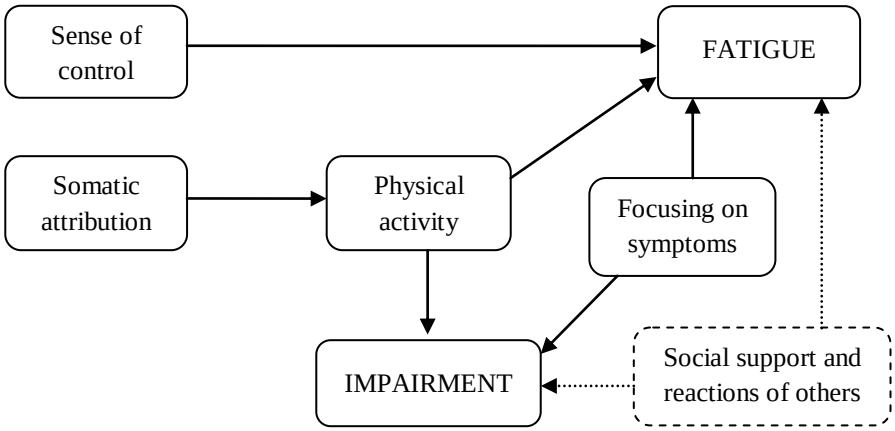
CHRONIC FATIGUE SYNDROME

CFS is characterised by severe fatigue which lasts for at least six months. Additional complaints such as pain, concentration problems and unrefreshing sleep are frequently reported. These complaints are not the result of a medical condition and lead to substantial impairment in areas such as physical, social and work related activities (Fukuda et al., 1994). Spontaneous recovery in CFS is uncommon, especially in patients with an illness duration of more than two years (van der Werf et al., 2002; Cairns & Hotopf, 2005). In the Netherlands, an estimated number of 30.000 to 40.000 people are suffering from CFS (Gezondheidsraad, 2005).

The aetiology of CFS is largely unknown but the differentiation between predisposing, precipitating and perpetuating factors has been fruitful in the past two decades, especially for the design of evidence-based interventions (Prins et al., 2006). Predisposing factors are factors that make people vulnerable to develop CFS, such as perfectionism or childhood maltreatment. Precipitating factors are factors that trigger somatic complaints, such as a viral infection or psychological stress. In most individuals, these complaints will stop as soon as the trigger has disappeared. In some people, especially those who are vulnerable to develop CFS, perpetuating factors can cause the persistence of the somatic complaints long after the initial trigger has disappeared.

Our research group has developed and tested a model of perpetuating factors which is depicted in figure 1. According to this model, the symptomatology of CFS patients is perpetuated by a low level of physical activity, which is caused by the tendency to attribute the symptoms to a somatic cause, a low level of perceived control over fatigue and a focus on symptoms (Vercoulen et al., 1998). Subsequent research has shown that a lack of social support and the reactions of others are relevant for the perpetuation of CFS as well (Prins et al., 2004).

Figure 1: Adaptation of the model of perpetuating factors introduced by Vercoulen et al. (1998).



COGNITIVE BEHAVIOUR THERAPY FOR CFS

Cognitive behavioural interventions are designed to intervene in the perpetuating factors of CFS (Sharpe et al., 1996; Deale et al., 1998; Prins et al., 2001). The treatment approach of our group is based on the insights of the model of perpetuating factors introduced by Vercoulen et al. (1998). In this variant of CBT for CFS, somatic attributions are discussed with the patient based on the medical examination report in which a somatic cause for the symptoms has been excluded (Bleijenberg et al., 2003; Knoop et al., 2010). The model of perpetuating factors is then discussed to enhance the patient's understanding of the role that cognitive and behavioural processes can play in the persistence of the symptoms. The treatment is divided into three parts.

In the preparation period, personalised goals are formulated. The overall goal of treatment is recovery in terms of impairment and fatigue severity (Knoop, 2007a). A regular pattern of bedtimes is then established to stop the disruption of the circadian rhythm. Next, cognitive techniques are introduced to teach patients how to recognise and challenge non-accepting and catastrophising thoughts which inhibit adequate coping. Patients are also taught how to decrease their focus on symptoms by distracting their attention from their fatigue. In addition, relatively active patients learn how to spread their activities more evenly across the day to avoid deregulation. Relatively active patients are characterised by bursts of activity followed by periods of prolonged rest (van der Werf et al., 2000). In contrast to these patients, pervasively passive patients have extremely low activity levels on virtually all days. These patients start with part two of the treatment directly after the cognitive interventions.

In the second part of treatment, the low level of physical activity is targeted by a gradual increase in walking or bicycling. Dysfunctional illness beliefs, such as the idea that even moderate levels of activity can do harm, are systematically challenged in this period. When patients have increased their level of physical activity appropriately (usually about 45 minutes twice a day), they are stimulated to realise their personal goals in part three of the treatment. These goals usually include the resumption of work, hobbies and other activities that imply recovery for the patient. While the increase in walking or bicycling was largely determined by the therapist, patients are now taking direct control of the gradual realisation of their personal goals to further increase the sense of control over symptoms. When the personal goals are realised, patients are stimulated to experiment with fluctuating bedtimes and levels of activity to further normalise the feeling of fatigue as part of an active and healthy life.

This cognitive behavioural strategy has been tested in adult and adolescent patients (Prins et al., 2001; Stulemeijer, 2005) and more recently also as low intensity variant in which self-guided instructions are accompanied by e-mail contact with a trained therapist (Knoop, 2008). All of these studies showed a significant effect of treatment on fatigue and impairment. Additional symptoms, such as pain and concentration problems, were also reduced (Knoop et al, 2007b; 2007c). These findings are in line with other randomised controlled trials (RCTs) about the efficacy of CBT for CFS (Sharpe et al., 1996; Deale et al., 1997; White et al., 2011). Several systematic reviews confirmed that CBT is an evidence-based intervention for the treatment of CFS patients (e.g. Price et al., 2008; Malouff et al., 2008; Bronwyn et al., 2011).

VALIDATION OF THE CBT FOR CFS MODEL

The basic idea of CBT for CFS is that a favourable change in the perpetuating factors will result in a reduction of symptomatology. Although past research has been testing extensively whether CBT yields a significant effect in CFS patients, it has remained unclear whether the perpetuating factors are actually changed by treatment and whether it is this change that can explain the decrease in symptomatology. An empirical test of these hypotheses can contribute substantially to the validation of current treatment models. A better knowledge about the mechanisms of change that are at work in CBT for CFS can also stimulate the development of more effective and efficient interventions for CFS patients in the future. Following the model of perpetuating factors (Vercoulen et al., 1998), three different mechanisms may characterise

effective interventions for CFS. First, the level of activity should be increased. Different opinions are held about why a change in activity may be beneficial. Some have argued that an increased level of physical activity reverses physical deconditioning (Fulcher et al., 1997; Wearden et al., 1998). Others have argued that a systematic increase in activity undermines avoidance behaviours which inhibit adaptive coping in CFS patients (Surawy et al., 1995; Deale et al., 1998). Such behaviours might be maintained through dysfunctional illness beliefs. A core belief of CFS patients is the assumption of having an uncontrollable disease. This belief is represented in the model of perpetuating factors by the factor sense of control over symptoms which should be increased as well.

Third, the focus on symptoms should be decreased. The underlying idea of this intervention is that dysfunctional cognitive processes can be disrupted by distracting attention. Task concentration training in social phobia, where patients learn how to pay attention to their surrounding instead of focusing on bodily symptoms such as blushing or sweating (Bögels et al., 2006), is based on the same idea. Moss-Morris et al. (2005) examined the mechanisms of change in graded exercise therapy (GET) for CFS. In GET, the level of physical fitness is increased on exercise equipment which has been shown to reduce symptomatology in CFS patients as well (Edmonds et al., 2004; Chambers et al., 2006). Although this intervention was designed to increase the level of fitness to reduce symptomatology, a decrease in focusing on symptoms mediated the effect of treatment in the study of Moss-Morris et al. (2005).

IMPLEMENTATION OF EVIDENCE-BASED PRACTICE FOR CFS

It has been mentioned before that CBT is an evidence-based intervention for CFS patients and that the course of symptomatology in these patients is generally sober without treatment (Cairns et al., 2005; Price et al., 2008; Malouff et al., 2008). The Dutch health council therefore concluded that CBT for CFS should also be delivered outside specialised therapy settings to increase treatment capacities and to reduce societal costs for medical consultation and sick leave (Gezondheidsraad, 2005). Our group has suggested national implementation of CBT for CFS in community-based mental health care centres (MHCs). In MHCs, sufficient cognitive behavioural therapists are available and somatic attributions are not further encouraged (Bleijenberg et al., 2000). Scheeres et al. (2006; 2008) examined the specific requirements for the implementation of CBT for CFS in MHCs and assembled an

implementation manual for future dissemination based on their findings. The basic idea was that a standardised implementation manual might enable MHCs to implement and sustain CBT for CFS independent of external implementation support which might be a considerable advantage for dissemination on a national level. The implementation manual describes the importance of training and supervision for therapists, of activities to inform potential referrers and patients about the new therapy, and of handling limited waiting periods.

The attempt to use limited treatment capacities optimally, has also stimulated efforts to develop a stepped care approach for CFS. A comparison of regular CBT and stepped care for CFS, in which a minimal intervention was combined with regular CBT, showed that stepped care is equally effective but more efficient than regular CBT alone (Knoop et al., 2008; Tummers et al., 2010). The minimal intervention consisted of guided self-instructions which were based on the same principles as regular CBT for CFS including contact with a trained therapist per e-mail (Bleijenberg et al., 2003; Knoop et al., 2008; Knoop et al., 2010).

POTENTIAL LIMITS OF EVIDENCE-BASED PRACTICE FOR CFS

Some patients experience such severe symptoms that they feel no longer able to leave their home. A member survey of a British patient organisation suggested that a considerable number of patients is actually bound to home due to their fatigue (Action M.E., 2001). While the validity of this survey may be the subject of methodological discussion, it is in fact striking that most research in the field of CFS has been conducted with patients who are able to follow outpatient treatment in some way. There is hardly any knowledge about the characteristics of patients who feel unable to engage in care as usual because of the severity of their symptoms. This lack of knowledge might implicate that our research findings do not generalise to all CFS patients. In addition, we might systematically marginalise a group of patients that is in strong need for effective interventions. More insight into the characteristics of homebound CFS patients and their demand for professional help is thus needed to close a potential scientific and clinical gap in the field of CFS.

OUTLINE OF THE THESIS

The Expert Centre for Chronic Fatigue of the Radboud University Nijmegen Medical Centre has been studying CFS and chronic fatigue in cancer survivors and chronic diseases for more than twenty years. Among other things, this research line has included the development and empirical study of CBT for CFS. Every year, several hundreds of patients who suffer from chronic fatigue consult the Expert Centre for assessment and treatment of their complaints. The purpose of this dissertation was to enhance the understanding of the mechanisms of successful change and implementation of CBT for CFS to further improve the quality of care for these patients.

Physical inactivity and the effect of CBT for CFS

A popular hypothesis about the mechanisms of change in effective treatment for CFS is the idea that patients need to get physically more active in order to feel less fatigued. The purpose of the study that is presented in *chapter 2* was to determine whether the effect of CBT on fatigue is actually mediated by a persistent increase in physical activity. Three RCTs about the efficacy of cognitive behavioural interventions for CFS (Prins et al., 2001; Stulemeijer, 2005; Knoop, 2008) were reanalysed according to the guidelines for mediation analysis of Baron and Kenny (1986). The hypothesised mediator physical activity was measured with Actometers in all studies which are small motion sensing devices that are worn around the ankle (van der Werf et al., 2000).

Maladaptive coping and the effect of CBT for CFS

It has also been suggested that CBT for CFS works because it changes maladaptive coping strategies. Most central to this hypothesis are avoidance behaviours and the focus on fatigue (Deale et al., 1998; Moss-Morris et al., 2005). The purpose of the study that is presented in *chapter 3* was to determine whether the effect of CBT for CFS on fatigue and impairment is mediated by a persistent decrease in avoidance of activity and aversive stimuli and a persistent decrease in the focus on fatigue. For this purpose, we reanalysed the largest of the previously mentioned RCTs (Prins et al., 2001) in which the maladaptive coping strategies were assessed with a coping questionnaire that is frequently used in the field of chronic pain. We examined the factor structure of the adapted coping questionnaire in our sample of CFS

patients and tested our mediation hypotheses according to the guidelines of Baron et al. (1986).

Towards an evidence-based treatment model

In *chapter 4*, we present the development of a treatment model for cognitive behavioural interventions focusing on CFS based on the model of perpetuating factors introduced by Vercoulen et al. (1998). We reanalysed the most recent of our RCTs for this purpose in which a minimal cognitive behavioural intervention was compared to a waiting list control group (Knoop et al., 2008). Structural equation modelling was used to test the treatment model in which cognitive processes were hypothesised to play a central role.

The implementation of CBT for CFS outside specialised settings

The purpose of the study that is presented in *chapter 5* was to determine whether CBT for CFS can be implemented and sustained by MHCs with the implementation manual introduced by Scheeres et al. (2006). For this purpose, we monitored the process data of three Dutch MHCs, one in which CBT for CFS was sustained from an earlier implementation study, one in which CBT was implemented as only intervention for CFS, and one in which CBT was implemented in the context of a stepped care program for CFS. The results of our MHCs were compared with the results from a previous benchmark study conducted by Scheeres et al. (2008).

Therapist effects and the dissemination of CBT for CFS

In *chapter 6*, we examined treatment outcome outside specialised settings. In particular, we focused on the role of therapists and their attitudes towards working with evidence-based treatment manuals. A scientific survey in the US has shown that the attitude of therapists towards standardised treatment manuals can vary considerably which may pose a problem to effective use of standardised treatment approaches (Addis et al., 2000). We used the routinely collected outcome data of our implementation study to test whether therapists would produce different outcomes and whether these differences might be explained by their attitude towards evidence-based treatment manuals.

Homebound CFS patients

The last study of this dissertation is presented in *chapter 7*. The purpose of that study was to determine whether homebound patients differ from other CFS patients on illness specific characteristics. For this purpose, we compared a group of homebound patients with the natural course condition of one of our outpatient RCTs (Prins et al., 2001). Illness specific characteristics included assessment of fatigue, impairment and additional complaints such as concentration problems, unrefreshing sleep and deterioration in psychological wellbeing. Physical inactivity, somatic attribution and lack of control over symptoms were also included. We hypothesised that the scores on these characteristics would be more problematic in homebound patients than in outpatients.

In *chapter 8*, the findings of the previous six chapters are discussed in more depth.

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2

How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity

Jan F Wiborg, Hans Knoop, Maja Stulemeijer, Judith B Prins & Gijs Bleijenberg
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ABSTRACT

Cognitive behaviour therapy (CBT) is known to reduce fatigue severity in chronic fatigue syndrome (CFS). How this change in symptomatology is accomplished is not yet understood. The purpose of the present study was to determine whether the effect of CBT on fatigue is mediated by an increase in physical activity. Three randomised controlled trials were reanalysed, previously conducted to evaluate the efficacy of CBT for CFS. In all samples, actigraphy was used to assess the level of physical activity prior and subsequent to treatment or a control group period. The mediation hypothesis was analysed according to guidelines of Baron and Kenny. A non-parametric bootstrap approach was used to test statistical significance of the mediation effect. Although CBT effectively reduced fatigue, it did not change the level of physical activity. Furthermore, changes in physical activity were not related to changes in fatigue. Across the samples, the mean mediation effect of physical activity averaged about 1% of the total treatment effect. This effect did not yield significance in any of the samples. The effect of CBT on fatigue in CFS is not mediated by a persistent increase in physical activity.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by severe and disabling fatigue which persists at least six months and which is not the result of a medical condition or ongoing exertion (Fukuda *et al.*, 1994). Cognitive behaviour therapy (CBT) has been shown to reduce fatigue severity and impairment in patients with CFS (Price *et al.*, 2008; Malouff *et al.*, 2008). This effect has often been attributed to an increase in activity because activity programs have traditionally played a central role in CBT for CFS (Sharpe *et al.*, 1996; Deale *et al.*, 1997; Bleijenberg *et al.*, 2003; Quarmby *et al.*, 2007). In the present study, we tested a treatment model in which the effect of CBT on fatigue is mediated by an increase in physical activity.

Several studies have demonstrated that the average level of physical activity in CFS patients is substantially lower than in healthy controls (e.g. van der Werf *et al.*, 2000; Black *et al.*, 2005). A low level of physical activity has also been shown to perpetuate the feeling of severe fatigue in patients with CFS (Vercoulen *et al*., 1998). In some approaches of CBT for CFS (e.g. Bleijenberg *et al*., 2003), an increase in physical activity is stimulated systematically by asking patients to take short walks on a daily basis which are gradually extended in duration up to twice an hour per day. Illness related cognitions are also targeted in these interventions. In particular, patients' preoccupation with their condition and the believe that they have little control over their symptoms are challenged. These cognitions have been found to perpetuate fatigue in CFS as well (Vercoulen *et al*., 1998).

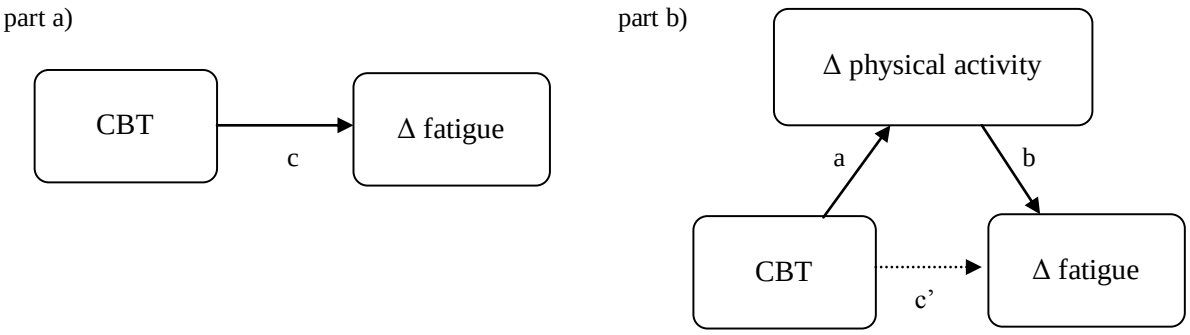
There are behavioural interventions for CFS which rely exclusively on a physical activity program to improve fatigue. According to the rationale of graded exercise therapy (GET), the key problem in CFS is physical deconditioning which can be overcome by enhancing the level of physical fitness (Fulcher & White, 1997; Wearden *et al.*, 1998). Patients are stimulated to gradually increase their level of physical activity on exercise bikes or other equipment. Illness related cognitions are not challenged intentionally. This strategy has been shown to reduce fatigue in CFS as well (Edmonds *et al.*, 2004; Chambers *et al.*, 2006).

By now, a substantial body of research is available to support the efficacy of interventions for CFS in which the level of physical activity is targeted. However, considerably less attention has been paid to whether the effect of these interventions actually depends on a change in physical parameters. Such a finding would be vital to the validation of all treatment models which rely on a physical activity program in some way to improve

fatigue. In the only study of such nature we are aware of, Moss-Morris *et al.* (2005) demonstrated that an increase in physical fitness does not contribute to the treatment effect of GET on fatigue in CFS.

The purpose of the present study was to determine whether the treatment effect of CBT on fatigue is mediated by an increase in physical activity. In psychotherapy research, testing mediation is a strategy to identify variables which intervene in the relationship between treatment and outcome and thereby help to better understand how treatment works (Frazier *et al*., 2004). This idea is illustrated in figure 1. In part a of figure 1, a change in fatigue is simply explained by the allocation of treatment (path c). This model is usually tested when the efficacy of an intervention is of primary interest to the investigator. In part b of figure 1, the effect of CBT on fatigue (path c') is mediated by a change in physical activity (path a) which is responsible for the change in fatigue (path b). We tested this mediation hypothesis to gain more insight into how CBT reduces fatigue in CFS.

Figure 1: The effect of CBT on fatigue without and with the hypothesised mediator changes in physical activity.



METHODS

For the purpose of the present study we reanalysed three randomised controlled trials (RCTs), previously conducted to test the efficacy of CBT on CFS (Prins *et al.*, 2001; Stulemeijer *et al.*, 2005; Knoop *et al.*, 2008). Treatment was based on the manual of CBT for CFS described in detail by Bleijenberg *et al.* (2003) and effectively reduced fatigue severity in all trials. Patients were randomly assigned to either a treatment or a control group condition. Assessment took place prior and subsequent to treatment or the control group period.

Samples

The first of the three RCTs evaluated the effect of CBT on CFS (Prins *et al.*, 2001). All patients were between 18 and 60 years of age and met the CDC research criteria for CFS (Fukuda *et al.*, 1994), except for the four additional symptoms criterion. In total, 270 patients were assigned to either CBT, a guided support group, or a natural course condition. CBT consisted of 16 sessions of 1hour over 8 months while the guided support group had 11 meetings of 1.5 hours over 8 months. All groups were assessed at baseline and 8 months later (second assessment). The results of the guided support group and the natural course condition were comparable in the original study (Prins *et al.*, 2001). We therefore approached the two control groups as one in our analyses.

The second RCT tested the effect of guided self-instructions on CFS (Knoop *et al.*, 2008). This minimal intervention consisted of written self-instructions combined with e-mail contact with a trained therapist. All patients were 18 years or older and met the 1994 CDC research criteria for CFS (Fukuda *et al.*, 1994). In total, 169 patients were assigned to either the guided self-instructions or a waiting list control condition. The time between baseline and second assessment varied between 6 and 12 months with a mean time of 10.5 months (*SD* = 4.0) in the treatment group and 9.7 months (*SD* = 3.6) in the control group.

The third RCT evaluated the effect of CBT in adolescents with CFS (Stulemeijer *et al.*, 2005). In total, 69 patients were assigned to either CBT or a waiting list condition. All patients were between 10 and 17 years of age and met the 1994 CDC research criteria for CFS (Fukuda *et al.*, 1994). Both groups were assessed at baseline and 5 months later (second assessment). CBT consisted of 10 sessions of 1 hour over 5 months. Parents of the adolescent patients were actively involved in the treatment process.

Instruments

Fatigue: The subscale fatigue severity of the Checklist Individual Strength (CIS) was used to indicate the severity of fatigue experienced by patients. It consists of eight items which are scored on a 7-point Likert scale. The sum score varies between 8, no fatigue, and 56, severe fatigue. The CIS is a reliable and valid instrument for the assessment of fatigue in CFS (Vercoulen *et al.*, 1994; Dittner *et al.*, 2004). A common cut-off score for severe fatigue is 35 (or higher) which is about two standard deviations above the norm score for healthy patients.

Physical Activity: Actigraphy was used to assess physical activity in all trials. The Actometer is a motion sensing device which is worn around the ankle for twelve consecutive days. An average daily level of physical activity is computed over this period with higher scores indicating more physical activity. The Actometer is described in more detail by van der Werf *et al.* (2000). They found a significant difference between the mean Actometer score of CFS patients which was 66 (*SD* = 22) and healthy controls who had a mean Actometer score of 91 (*SD* = 25). They also identified a group of patients who scored below the mean score of CFS patients on eleven out of twelve days and labelled this group as pervasively passive. We excluded all patients from our study who missed actigraphy at second assessment.

Analyses

We conducted one-way ANOVA's to test whether those patients who were excluded from our study due to missing actigraphy at second assessment differed on baseline characteristics from those patients who were included. Fisher's exact test was used in case of dichotomous dependent variables.

A macro expansion for SPSS introduced by Preacher and Hayes (2004) was employed to conduct mediation analysis. The macro followed the standard for mediation analysis introduced by Baron & Kenny (1986). Paths a, b, c and c' of figure 1 were analysed using regression analysis. To examine path a, changes in physical activity were regressed on treatment. Path b was examined by regressing changes in fatigue on changes in physical activity, correcting for treatment. In case of path c, changes in fatigue were regressed on treatment, while path c' was examined by regressing changes in fatigue on treatment, this time correcting for the mediator changes in physical activity. The size of the mediation effect was computed by multiplying path a with path b.

Statistical significance of the mediation effect was tested using a non-parametric bootstrap approach (Preacher et al., 2004). The observed dataset was randomly resampled 5000 times with replacement which resulted in 5000 samples with mediation effect. The mean of these mediation effects was used as population parameter. When the 95% confidence interval around this parameter did not include zero, the null hypothesis was rejected. When the 95% confidence interval did include zero, the mediation hypothesis was rejected. This

procedure increased the power to detect significant effects in small, non-normally distributed samples.

We analysed each trial separately because patient population (adult vs. adolescent) as well as presentation of treatment (face to face contact vs. guided self-instructions) differed considerably between the trials. Since we examined three individual trials in one study, we preferred a p-value of $\leq .017$ as threshold for significance (.050 divided by 3). All change scores were computed by subtracting second from baseline assessment. A negative change score indicated decrease while a positive one indicated increase on the respective variable.

RESULTS

In table 1, the baseline characteristics of the patients who were included in our study are compared with those patients who were excluded due to missing actigraphy at second assessment. As shown, none of the differences between these two groups yielded significance in our analyses.

Table 1: Baseline characteristics of included versus excluded patients.

	Prins		Knoop		Stulemeijer	
	included	*excluded*	*included*	*excluded*	*included*	*excluded*
n (CBT)	211 (70)	59 (22)	132 (58)	37 (26)	58 (28)	11 (7)
age*	36.9 (10.2)	36.0 (9.7)	37.9 (10.4)	38.4 (10.1)	15.7 (1.3)	15.4 (0.8)
p	.543		.785		.493	
% female (*n*)	78 (165)	80 (47)	77 (101)	89 (33)	90 (52)	81 (9)
*p***	.860		.111		.604	
illness duration*	5.5 (5.4)	6.0 (6.3)	9.7 (9.9)	12.0 (10.9)	1.8 (1.3)	1.7 (1.2)
p	.566		.213		.865	
fatigue severity	52.0 (4.1)	52.9 (3.4)	49.6 (5.4)	49.2 (5.4)	51.8 (4.3)	53.4 (2.7)
p	.118		.692		.251	
physical activity	65.4 (20.4)	69.0 (26.7)[1]	63.3 (22.5)	61.9 (18.5)	65.3 (21.0)	65.7 (33.2)
p	.272		.733		.953	
% passive (*n*)	25 (53)	14 (8)	27 (35)	24 (9)	22 (13)	44 (4)[2]
*p***	.077		1.00		.216	

Note. Unless otherwise indicated, all data are mean scores (SD) and differences were examined with ANOVA.
*In years. **Fischer's exact test. [1]One patient missing. [2]Two patients missing.

In table 2, baseline, second assessment and change scores on fatigue severity and physical activity are presented per treatment condition for the group of included patients.

Table 2: Mean baseline, second assessment and change scores (*SD*) on fatigue severity and physical activity in the group of included patients per treatment condition.

	Prins (n=211)		Knoop (n=132)		Stulemeijer (n=58)	
treatment condition	CBT (n=70)	control (n=141)	CBT (n=58)	control (n=74)	CBT (n=28)	control (n=30)
fatigue severity						
baseline	52.4 (4.0)	51.7 (4.1)	49.5 (5.1)	49.6 (5.7)	52.3 (4.1)	51.3 (4.4)
second assessment	40.3 (10.5)	45.8 (8.7)	38.9 (10.8)	45.7 (8.9)	24.8 (14.1)	42.9 (13.9)
change score	-12.1 (10.3)	-6.0 (9.2)	-10.6 (11.1)	-3.9 (8.4)	-27.5 (14.2)	-8.4 (13.4)
physical activity						
baseline	67.4 (21.8)	64.5 (19.7)	63.1 (23.5)	63.5 (21.8)	65.6 (22.4)	65.0 (20.1)
second assessment	68.8 (25.2)	64.9 (21.7)	67.3 (22.5)	67.8 (21.4)	75.8 (21.7)	67.7 (23.8)
change score	1.4 (18.5)	0.4 (16.4)	4.3 (20.4)	4.3 (21.0)	10.3 (21.7)	2.7 (28.1)

In table 3, it can be seen that fatigue was reduced significantly more in the treatment group than in the control group in all samples (path c). However, CBT did not produce a significant change in physical activity in any of the samples (path a).

Table 3: Testing paths a, b, c and c' as depicted in figure 1.

	path a	*path b*	*path c*	*path c'*
Prins				
B	0.99	-0.04	-6.11	-6.07
SE	2.50	0.04	1.40	1.40
t	0.40	-1.07	-4.36	-4.33
p	.693	.285	<.001	<.001
Knoop				
B	-0.00	-0.08	-6.64	-6.64
SE	3.64	0.04	1.70	1.68
t	-0.00	-2.00	-3.91	-3.95
p	.999	.047	<.001	<.001
Stulemeijer				
B	7.58	-0.10	-19.10	-18.35
SE	6.63	0.07	3.63	3.64
t	1.14	-1.40	-5.27	-5.04
p	.257	.178	<.001	<.001

There was also no significant relationship between changes in physical activity and changes in fatigue (path b). The effect of treatment on fatigue remained significant when it was controlled for changes in physical activity (path c').

In table 4, results of the bootstrap analysis are shown. Resampling of the observed data set resulted in a mean mediation effect with a 95% confidence interval for each sample. The mean mediation effect averaged about 1% of the total treatment effect across the three samples. The 95% confidence interval of the mean mediation effect included zero in all samples. The mediation hypothesis was not confirmed.

Table 4: Testing the mediation effect according to the Bootstrap approach.

	Prins	Knoop	Stulemeijer
mean mediation effect	-0.03	0.01	-0.61
Lower CI (95%)	-0.39	-0.69	-2.19
Upper CI (95%)	0.27	0.76	0.86
% total treatment effect	0.5	-0.15	3.2

DISCUSSION

The data did not support a treatment model in which the effect of CBT on fatigue is mediated by an increase in physical activity. CBT did neither cause an increase in physical activity at the end of treatment (path a) nor was an increase in physical activity associated with a reduction in fatigue (path b). A formal test of the mediation effect confirmed that CBT yielded its effect independent of a persistent change in physical activity.

These results are in line with the study of Moss-Morris *et al.* (2005) in which was demonstrated that not an increase in fitness but a change in preoccupation with symptoms mediated the effect of GET on fatigue. The results are also consistent with earlier research on CBT for CFS in which a reduction in fatigue was associated with a change in illness beliefs (Deale *et al.*,1998). In the light of these findings, changing illness related cognitions seems to play a more crucial role in CBT for CFS than an increase in physical activity.

There are several potential alternative explanations for the fact that we did not find support for our mediation hypothesis. A substantial amount of patients did not complete actigraphy at second assessment and had to be excluded from our mediation analyses. It is

possible that we introduced a bias through exclusion which might account for our findings. However, analysis of the baseline characteristics revealed that a selection bias is no likely explanation for our findings.

Our patients were not required to stick to their physical activity program until the end of therapy. As treatment proceeded, they were allowed to substitute physical activities for other activities such as social ones. Consistently, treatment could have resulted in a temporary increase in physical activity which was no longer existent when second assessment took place. This temporary increase in physical activity during treatment might have been sufficient to facilitate a persistent change in illness related cognitions. When patients learned that they were able to increase their level of physical activity despite of their symptoms, their believe of having little control over their condition should have changed and with it also the perception of fatigue as an inherently aversive state. To examine these mechanisms of change in CBT for CFS, patients' physical activity and illness related cognitions need to be monitored repeatedly during treatment.

Patients with a pervasively passive activity pattern have extremely low levels of physical activity. These patients do not respond to common CBT for CFS (Prins *et al.*, 2001). A specifically tailored approach in which the physical activity program is delivered earlier showed better effects for these patients (e.g. Stulemeijer *et al*., 2005). They might thus profit from a persistent increase in physical activity after all. Unfortunately, the number of patients was too small to properly examine whether a change in physical activity does mediate the effect of treatment in pervasively passive patients.

In contrast to pervasively passive patients, the majority of CFS patients is not only characterised by a low level of physical activity, but has also a deregulated pattern of physical activity in which short periods of high activity are alternated with longer periods of rest (van der Werf *et al.*, 2000). These patients were taught to spread their activities evenly across day and week (Bleijenberg *et al*., 2003). Perhaps a change in activity regulation is more important to facilitate improvement in relatively active CFS patients than an increase in physical activity.

Taking these considerations into account, the exact role of physical activity in CBT for CFS remains to be determined. Besides physical activity, future investigations should also examine the role of changes in social, mental and work related activities in CBT for CFS,

preferably based on the time patients actually spend on these activities to limit perception bias. For the time being, our study was the first one to show that the severity of fatigue in patients with CFS is not reduced by CBT because patients have become more physically active at the end of their treatment. Based on these findings, physical activity programs can better be understood as a way to facilitate change in other mechanisms which are more directly related to a change in fatigue. Among these mechanisms, a change in illness related cognitions is likely to play a crucial role in CBT for CFS and should therefore be monitored closely during treatment.

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3

Does a decrease in avoidance behaviour and focusing on fatigue mediate the effect of cognitive behaviour therapy for chronic fatigue syndrome?

Jan F Wiborg, Hans Knoop, Judith B Prins & Gijs Bleijenberg
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ABSTRACT

Cognitive behaviour therapy (CBT) leads to a significant reduction in fatigue severity and impairment in patients with chronic fatigue syndrome (CFS). The purpose of the present study was to determine whether the effect of CBT for CFS on fatigue and impairment is mediated by a decrease in avoidance behaviour and focusing on fatigue. For this purpose, we reanalysed a randomised controlled trial which was previously conducted to test the efficacy of CBT for CFS. Two-hundred nineteen patients completed assessment prior and subsequent to treatment or a control group period. Mediation analysis revealed that a decrease in focusing on fatigue mediated the effect of CBT for CFS on fatigue and impairment. Avoidance of activity and avoidance of aversive stimuli were not significantly changed by treatment and were therefore excluded from mediation analysis. A decrease in the focus on fatigue seems to contribute to the treatment effect of CBT for CFS.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by severe and disabling fatigue which persists at least six months and which is not the result of a medical condition or ongoing exertion (Fukuda et al., 1994). Additional symptoms such as pain, concentration problems and postexertional malaise are frequently reported. According to the cognitive behavioural model for CFS (Surawy et al., 1995; Prins et al., 2006), patients fail to cope adequately with a period of somatic illness or psychological stress which causes the perpetuation of their symptoms. For example, Vercoulen et al. (1998) found that CFS patients who believe that their symptoms are due to an ongoing medical condition are also more likely to engage in less physical activity which was associated with higher levels of fatigue and impairment. Other factors which contributed to higher levels of symptomatology in their model of perpetuating factors were higher levels on focusing on symptoms and lower levels on sense of control over the complaints. Cognitive behaviour therapy (CBT) intervenes in the perpetuating factors for CFS by gradually increasing the level of activity and systematically challenging illness-related believes (Sharp et al., 1996; Deale et al., 1997; Bleijenberg et al., 2003). This strategy has been shown to be effective in reducing fatigue severity, impairment and additional complaints in CFS patients (Malouff et al., 2008; Price et al., 2008).

Despite the fact that CBT for CFS is by now an evidence-based intervention, it is not yet well understood through which mechanisms of change this intervention works. Deale et al. (1998) found that good outcome in CBT for CFS is associated with less avoidance behaviour but not with less somatic attributions. Whether the effect of the intervention was actually mediated by a decrease in avoidance behaviour was not tested in this study. Mediation is the process in which one or more variables (the hypothesised mediators) intervene in the relationship between treatment en outcome (Baron & Kenny, 1986; Frazier et al., 2004). In mediation analysis, the mechanisms of change of psychological interventions are identified. This analytic strategy can substantially contribute to the validation of treatment models and the enhancement of clinical practice (Kraemer et al., 2002).

Moss-Morris et al. (2005) conducted a mediation analysis in which the mechanisms of change in graded exercise therapy (GET) were analysed. GET for CFS is a behavioural intervention in which patients gradually increase their level of fitness, for example on exercise bikes. Illness beliefs are not challenged explicitly. Their mediation analyses showed that GET

did not lead to the hypothesised increase in physical fitness but a decrease in the focus on symptoms which mediated the effect of their intervention. Similarly, Wiborg et al. (2010) were unable to find a persistent increase in physical activity in three randomised controlled trials (RCTs) of CBT for CFS.

In the present study, we were interested in whether decreases in avoidance behaviour and focusing on symptoms might mediate the effect of CBT for CFS. For this purpose, we reanalysed a RCT which was previously conducted by our research group to test the efficacy of CBT for CFS (Prins et al., 2001). The intervention was based on the CBT for CFS manual described by Bleijenberg et al. (2003) and was more effective in reducing fatigue severity and impairment than two control group conditions. We hypothesised that a decrease in avoidance behaviour and focusing on fatigue would mediate the effect of our intervention.

METHODS

Sample

In total, 270 patients were randomly assigned to either CBT or one of two control group conditions. CBT consisted of 16 one-hour sessions spread over a period of 8 months. In the first control group, patients received 11 one-and-a-half-hour meetings of non-directive counselling spread over a period of 8 months. In the second control group, patients received no intervention and were free to do whatever they found appropriate. The results of the two control groups were similar in the original trial (Prins et al., 2001). We therefore approached the two control groups as one in our analyses (see also Wiborg et al., 2010).

All groups were assessed before treatment or the control group period had started (baseline), 8 months later when treatment or the control group period had been finished (second assessment) and at 6 months follow-up (i.e. 14 months after baseline assessment). In the present study, we concentrated on the mechanisms of change between baseline and second assessment which was accomplished at the end of treatment. Fifty-one patients did not complete second assessment of the coping strategies and were excluded from the present study. The mean age of the remaining 219 patients was 36.9 years (SD= 10.2) and 79% of them was female. The mean illness duration was 5.5 years (SD= 5.5). All patients met the CDC research criteria for CFS (Fukuda et al., 1994), except for fourteen patients who did not have four or more additional symptoms.

Instruments

Coping Strategies: We modified the Pain Coping Inventory (Kraaimaat & Evers, 2003) by substituting the word fatigue for pain and selected all items of the second order factor *passive coping*, which reflects the tendency to restrict functioning and think negative about the symptoms (table 1).

Table 1: The validation of avoidance behaviour and focusing on fatigue (N=267).

factor	When I feel fatigued I ...	loading
avoidance of activity ($\alpha = 0.72$)	...stop with my activities.	.56
	...confine myself to simple activity	.60
	...do not exert myself physically.	.74
	...rest, sitting or lying down.	.73
	...take a comfortable posture.	.63
avoidance of aversive stimuli ($\alpha = 0.73$)	...make sure that I do not get upset.	.43
	...search for a restful environment to retreat.	.72
	...avoid bothering sounds.	.69
	...avoid light.	.58
	...am careful of what I eat or drink.	.48
	...separate myself.	.65
	...try to return home as soon as possible.	.58
focusing on fatigue ($\alpha = 0.80$)	...focus on the fatigue all the time.	.59
	...think of all the things that remain undone because of the fatigue.	.72
	...start to worry.	.76
	...wonder about the cause of the fatigue.	.74
	...think that the fatigue will get worse.	.67
	...think about moments which were free from fatigue.	.59
	...think I will go mad because of the fatigue.	.49
	...think that others do not understand what it is to have such fatigue.	.45

Note. Only loadings of $\geq$.40 are shown.

Because this modification has not been validated before, we conducted a Principal Component Analysis (PCA) in our sample resulting in three independent factors which were named *avoidance of activity*, *avoidance of aversive stimuli*, and *focusing on fatigue* (table 1). This structure is identical with the findings of Kraaimaat et al. (2003), with the exception of one item (the self-administration of physical stimuli) which was excluded because it did not load substantially on any of our factors (i.e. <.40).

All items were scored on a 4-point Likert scale varying between 1, seldom or never, and 4, very often. Higher sum scores indicated more avoidance of activity, avoidance of aversive

stimuli and focusing on fatigue. The sum scores on the individual scales vary between 5 and 20 in the case of avoidance of activity (5 items), 7 and 28 in the case of avoidance of aversive stimuli (7 items) and 8 and 32 in the case of focusing on fatigue (8 items). The internal consistency of the individual scales was satisfactory (table 1). All three factors were significantly related to each other (table 2).

Table 2: Pearson's correlation coefficients (N=267).

	avoidance of activity	avoidance of aversive stimuli
avoidance of aversive stimuli	.42	
focusing on symptoms	.20	.26

Note. All coefficients were significant at p≤.001.

Fatigue: The subscale fatigue severity of the Checklist Individual Strength (CIS) was used to indicate the level of fatigue during the last two weeks. All items of the CIS were scored on a 7-point Likert scale. The sum score of the subscale fatigue severity (8 items) varies between 8, no fatigue, and 56, severe fatigue. The CIS is a reliable and valid instrument which has been shown to be sensitive for changes over time (Vercoulen et al., 1994). The internal consistency of the fatigue severity subscale has been found to be good with a Cronbach's alpha of 0.88. The cut-off score for severe fatigue was 40 or higher in this study.

Impairment: The level of impairment was measured with the Sickness Impact Profile (Bergner et al., 1981) which has good reliability and content validity. A total score was calculated by addition of the weights of items (range 0–5799) in eight subscales: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work, and recreation (Prins et al., 2001).

Analyses

We conducted two multivariate general linear models (GLM) to test the differences at baseline assessment between included versus excluded patients and to test whether treatment actually changed the coping strategies of our patients. To correct for type I errors (i.e.

incorrect rejection of true null hypotheses), we only took significant differences on the univariate tests into account when the multivariate test yielded significance as well. Following the widely accepted standard of Baron et al. (1986) for mediation analysis, we excluded all coping strategies from further analysis which were not significantly affected by CBT according to our GLM.

A macro extension for SPSS introduced by Preacher and Hayes (2004) was used to test our mediation hypotheses. At first, the effect of treatment on outcome was tested (a). Second, the effect of treatment on the hypothesised mediator was tested (b). Third, the effect of the hypothesised mediator on outcome was tested, corrected for treatment (c). Thereafter, the effect of treatment on outcome was tested again, this time corrected for the hypothesised mediator (a'). If all of these effects, including a', were significant all preconditions for partial mediation were fulfilled (Baron et al., 1986). If all of these effects, except path a', were significant all preconditions for complete mediation were met. All of these tests were conducted using regression analysis. Change scores (second minus baseline assessment) were used for all outcome and mediator variables.

A non-parametric bootstrap approach was used to estimate the extent to which the effect of our intervention was actually mediated by a change in coping and to test for the statistical significance of the mediation effect (Preacher et al., 2004). In the bootstrap approach, population parameters are generated empirically instead of relying on normal theory. This approach leads to more power to detect significant effects even in small, non-normally distributed samples. A mean mediation effect with a 95% confidence interval was generated by randomly resampling the observed dataset 1000 times with replacement. The null hypothesis was rejected when this 95% confidence interval did not include zero. This procedure equals the $p \leq .05$ standard in normal theory testing which was used as threshold for significant findings in the multivariate GLM's as well.

RESULTS

Differences on baseline assessment due to exclusion

Multivariate testing of the baseline differences on fatigue, impairment and coping due to exclusion did not yield significance (table 3). Univariate differences were therefore not further tested.

Table 3: Testing the mean differences at baseline assessment on fatigue, impairment, and coping due to exclusion.

	included	excluded	*F*	*p*
n (CBT)	219 (73)	51 (19)		
multivariate				
Wilks-Lambda	0.97		1.72	.131

Note. Three excluded patients did not complete baseline assessment as well.

Selecting potential mediators of the treatment effect of CBT for CFS

The multivariate test of the treatment effect on changes in coping was significant (table 4). Univariate testing revealed that the focus on fatigue decreased significantly more in the treatment group than in the control group. The effect of treatment on avoidance of activity and avoidance of aversive stimuli was not significant. Avoidance behaviour was therefore excluded from further analyses.

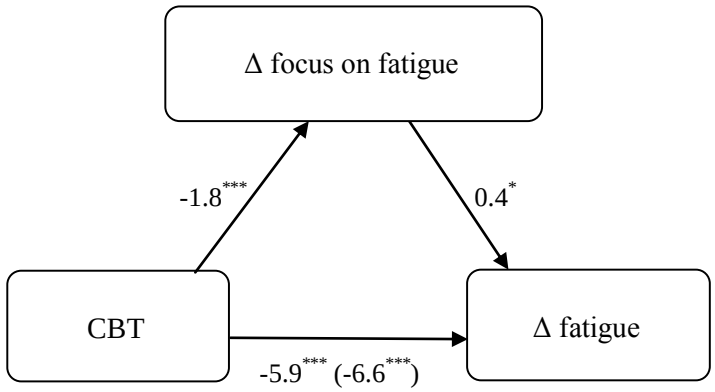
Table 4: Testing the effect of treatment (CBT vs. control) on changes in coping (*SD*) (N=219).

	treatment	control	*F*	*p*
multivariate				
Wilks-Lambda	0.94		4.40	.005
univariate				
Δ avoidance of activity	-0.5 (2.5)	-0.4 (2.3)	0.09	.762
Δ avoidance of stimuli	-1.0 (3.8)	-0.6 (3.2)	0.94	.333
Δ focusing on fatigue	-3.2 (3.6)	-1.4 (3.3)	13.0	$\leq$.001

Testing the mediation effect of changes in focusing on fatigue

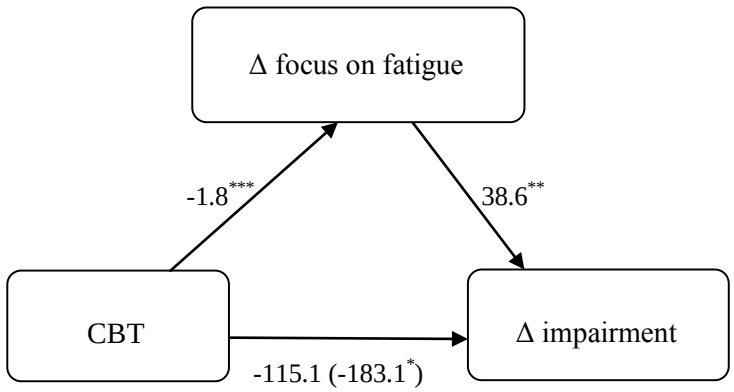
Analysis of the effects a, b, c, and a' showed that all conditions for partial mediation were met in the case of fatigue (figure 1). In the case of impairment, all conditions for complete mediation were met (figure 2). According to the bootstrap approach, the mean mediation effect on fatigue was -0.74 with a lower confidence interval of -1.89 and an upper confidence interval of -0.08. The effect of treatment on fatigue was significantly mediated by a decrease in focusing on fatigue. The same accounted for the mean mediation effect on impairment which was -67.92, with a lower confidence interval of -165.45 and an upper confidence interval of -21.01.

Figure 1: Regression coefficients as derived with the macro of Preacher & Hayes for fatigue (the value in parentheses represents the effect of CBT on fatigue without correction for the mediator).



Note. *p≤ .05. **p≤ .01. ***p≤ .001. All effects are unstandardised.

Figure 2: Regression coefficients as derived with the macro of Preacher & Hayes for impairment (the value in parentheses represents the effect of CBT on impairment without correction for the mediator).



Note. *p≤ .05. **p≤ .01. **p≤ .001. All effects are unstandardised.

DISCUSSION

The purpose of the present study was to determine whether the treatment effect of CBT for CFS is mediated by a decrease in avoidance behaviour and focusing on fatigue. As hypothesised, we found support in favour of a treatment model in which the level of fatigue and impairment were reduced because patients had decreased their focus on fatigue. This finding is in line with a study conducted by Moss-Morris et al. (2005) in which a change in focusing on symptoms mediated the effect of GET for CFS. To our knowledge, our study is

the first one to show that a decrease in the focus on fatigue also contributes to the reduction of fatigue and impairment in CBT for CFS.

This finding is also in accordance with a recent review in which we argued that cognitive processes are likely to play a central role in the perpetuation and treatment of CFS (Knoop et al., 2010). One of these processes is the tendency to focus on the fatigue. In CFS patients, this tendency could be a difficulty to disengage from the symptoms which is also seen in depressive disorders in the form of rumination (Caseras et al., 2007). However, it might also be a form of hypervigilance which is a state of abnormally increased arousal and responsiveness to certain stimuli also found in anxiety disorders (Caseras et al., 2008). An inspection of the factor loadings of our focusing scale suggests that we have primarily tested the ruminative character of this concept. More research is needed to unravel the exact nature of the focus on symptoms in CFS patients, including methods which assess attentional processes experimentally (Knoop et al., 2010).

Contrary to our hypothesis that a decrease in avoidance of activity and aversive stimuli would also mediate the effect of our intervention, we found no significant effect of treatment on avoidance behaviour. Several explanations may account for this finding which can also be understood as limitations of our study. First, we simply may have missed a temporary change in avoidance behaviour because we had no assessment during treatment. Such a temporary change might have been sufficient to facilitate improvement and may have been no longer relevant once the level of fatigue had been decreased. Advanced data about the mediating variables while treatment is proceeding are needed to enhance the understanding of the exact sequences of change in CBT for CFS.

Next, we did not differentiate between patients with a fluctuating active and patients with a pervasively passive activity pattern (van der Werf et al., 2000). Fluctuating active patients are characterised by bursts of activity which are followed by periods of prolonged rest. Pervasively passive patients are characterised by low levels of physical activity on virtually all days. Avoidance behaviour may be more problematic in pervasively passive patients because they are more likely to fear that even moderate levels of activity can cause damage to their body. More research with higher numbers of these patients is needed to test whether they may actually profit from a reduction in avoidance behaviour.

Some more comment on our instrumentation seems appropriate as we used a coping inventory which has not been validated outside pain studies before. Although the factor structure of the scale appeared to be robust, we know little about how it relates to other fatigue related constructs. Furthermore, our focusing on fatigue scale seems to include items of other cognitive processes such as catastrophising (i.e. I think that I will go mad because of the fatigue). These concepts should be examined separately to further differentiate between the various cognitive processes which are supposed to play a role in CBT for CFS. Besides the before mentioned processes, promising candidates for a mediating effect between treatment and outcome are (changes in) a low self-efficacy with respect to the fatigue and dysfunctional beliefs about one's own ability to be active (Knoop et al., 2010).

Finally, clinical practice has been refined since our trial has been conducted about ten years ago which may limit the generalisability of our findings with respect to present cognitive behavioural interventions for CFS. For example, we modified our treatment manual in order to be more responsive to pervasively passive patients who responded poorly to treatment in this trial. This modification has brought an increase in treatment effect (Stulemeijer et al., 2005). Hence, the active ingredients of CBT for pervasively passive CFS patients might be more adequately addressed in recent trials. Yet, independent of these and other considerations, we do not expect that the central mechanisms of change at work in CBT for CFS have changed fundamentally over time.

In summary, our findings provide first support for the idea that CBT for CFS can profit from interventions which target the focus on symptoms. In treatment, patients should learn to accept prevalent feelings of fatigue and train their ability to distract their attention from their complaints to facilitate improvement, for example by focusing on activity or aspects of the environment. Our findings may also implicate that continuous registration of the complaints can be disadvantageous because patients are encouraged to focus on their symptoms.

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4

Towards an evidence-based treatment model for cognitive behavioural interventions focusing on chronic fatigue syndrome

Jan F Wiborg, Hans Knoop, Laurence E Frank & Gijs Bleijenberg
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ABSTRACT

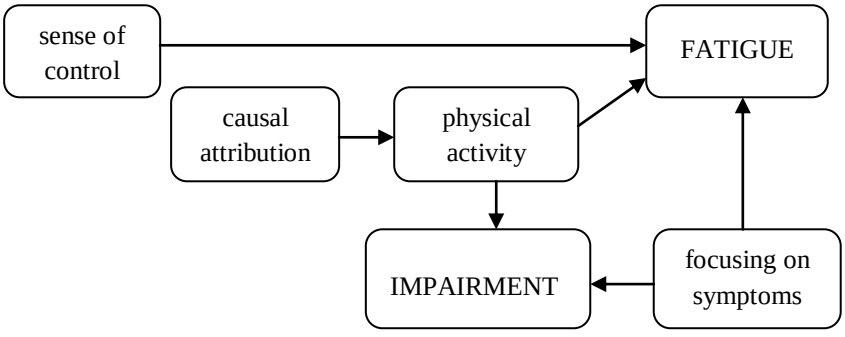
The purpose of the present study was to develop a treatment model for cognitive behavioural interventions focusing on chronic fatigue syndrome (CFS) based on the model of perpetuating factors. For this purpose, we reanalysed the data of a previously conducted randomised controlled trial in which a low intensity cognitive behavioural intervention was compared to a waiting list control group. Structural equation modelling was used to test a treatment model in which changes in focusing on symptoms, perceived problems with activity, and sense of control over fatigue were hypothesised to mediate the effect of our intervention on fatigue severity and disability. In the final model, which had a good fit to the data, the effect of treatment was mediated by a decrease in perceived problems with activity and an increase in sense of control over fatigue. Our findings suggest that cognitive behavioural interventions for CFS need to change the illness perception and beliefs of their patients in order to be effective.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by severe and disabling fatigue which persists at least six months and which cannot be explained medically (Fukuda et al., 1994). Cognitive behavioural interventions have been shown to be effective in reducing the symptomatology of CFS patients (Malouff et al., 2008; Price et al., 2008). These interventions usually incorporate a program in which the level of activity is gradually increased while dysfunctional beliefs are systematically challenged (Sharp et al., 1996; Deale et al., 1997; Bleijenberg et al., 2003; Quarmby et al., 2007). It is a widely accepted premise that the treatment effect of these interventions can be attributed to these ingredients, but empirical studies on the exact mechanisms of change are scarce and typically limited to the validation of one active ingredient per study. The purpose of the present study was to develop a more comprehensive model for cognitive behavioural interventions focusing on CFS.

Different cognitive behavioural models exist that seek to explain the persistence of symptomatology in CFS patients (Wessely et al., 1989; Surawy et al., 1995; Fry& Martin, 1996; Vercoulen et al., 1998; Gaab, 2004). All of these approaches generally agree on the fact that illness-specific beliefs and behaviours perpetuate the suffering of these patients and that effective treatment needs to intervene in the perpetuating factors to facilitate improvement. In figure 1, we present the work of Vercoulen et al. (1998), who introduced an empirically supported model of perpetuating factors for CFS. This model served as basis for the development of our treatment model. In the model of Vercoulen et al. (1998), a combination of being physically inactive, lacking sense of control over fatigue and focusing on symptoms perpetuates severe fatigue and impairment. The low level of physical activity is caused by predominant somatic attributions.

Figure 1: Model of perpetuating factors introduced by Vercoulen et al. (1998).



Several studies have tested the role of these perpetuating factors in facilitating improvement. A study by Deale et al. (1998) showed that somatic attributions of CFS patients are not affected by cognitive behaviour therapy (CBT). Without such a change, a factor cannot account for the effect of treatment (Baron & Kenny, 1986; Frazier et al., 2004). This finding is also in accordance with the model of perpetuating factors in which causal attributions are not directly linked to fatigue or impairment (Vercoulen et al., 1998). Consequently, we excluded this variable from further examination.

The role of activity is more complex. In the model of Vercoulen et al. (1998), the persistence of fatigue and impairment is caused by a low level of physical activity which suggests that patients need to get physically more active in order to improve. Two studies tested this hypothesis. Moss-Morris et al. (2005) examined whether the effect of graded exercise therapy (GET) can be explained by a change in physical fitness. Although patients gradually increased their level of physical activity on exercise equipment in this study, the treatment effect was not mediated by a change in physical fitness. In the second study, Wiborg et al. (2010) examined three randomised controlled trials (RCTs) to test whether the effect of CBT for CFS can be explained by an increase in Actometer scores. Actometers are motion sensing devices which are frequently used to assess physical activity in CFS patients. They found that the effect of treatment was not mediated by a change in these scores. In other words, an increase in physical activity was not responsible for the treatment effect in any of these studies.

It is vital to notice in this context that Vercoulen et al. (1998) assessed physical activity with self-rating scales in their model of perpetuating factors which are known to be receptive to cognitive biases. Knoop et al. (2010) have argued that such biases are central to the perpetuation of CFS. In particular, patients with CFS tend to perceive substantial problems with activity independent of their objective performance and interpret these problems as inherent feature of an uncontrollable illness. A change in perceived problems with activity through activity programs may, in turn, correct the belief that CFS is an uncontrollable illness and thereby help to relieve symptomatology. This would also be in accordance with a study by Deale et al. (1998), who found that a change in activity-related beliefs was associated with improvement in CBT for CFS.

To our knowledge no comparable study has been conducted with control-related beliefs in the context of CFS, but an increase in sense of control has been shown to be a powerful mediator of the treatment effect of CBT for chronic pain (Turner et al, 2007). A comparable finding in the context of CFS would be in accordance with the model of perpetuating factors (Vercoulen et al., 1998), which suggests that an increase in sense of control over fatigue should lead to lower levels of fatigue.

The remaining factor of the Vercoulen et al. (1998) model is focusing on symptoms. Two mediation studies examined the role of this factor, one in GET for CFS (Moss-Morris et al., 2005) and one in CBT for CFS (Wiborg et al, 2011). A decrease in focusing on symptoms was a significant mediator of the treatment effect in both studies.

Based on these insights, we included focusing on symptoms, perceived (i.e. self-reported) problems with activity, and sense of control over fatigue into our search for a more comprehensive treatment model for cognitive behavioural interventions focusing on CFS. We reanalysed the most recent of the RCTs that were examined in the study by Wiborg et al. (2010) for this purpose. The original study was conducted by Knoop et al. (2008) and compared a low intensity cognitive behavioural intervention with a waiting list control group. Levels of fatigue severity and disability were significantly decreased by this intervention.

METHODS

Sample and Intervention

For a detailed description of the original trial we refer the reader to Knoop et al. (2008). In the present study, 30 of the 169 patients that were included in the original trial were excluded because they did not complete the second assessment of the hypothesised mediators (see also Wiborg et al., 2010). The mean age of the remaining 139 patients was 37.8 years (SD = 10.4). The median illness duration was 7 years, with a minimum of 1 and a maximum of 35 years. One hundred and eight patients (78%) were female. Sixty-four patients (46%) received the guided self-instructions. Treatment was delivered in accordance with the manual of Bleijenberg et al. (2003) which was based on the model of perpetuating factors discussed earlier (Vercoulen et al., 1998). Instead of face-to-face contact, the intervention relied on written self-instructions combined with e-mail contact with a trained therapist. The intervention included goal setting, fixed sleep wake cycles, reducing the focus on bodily

symptoms, the systematic challenge of fatigue-related beliefs, the regulation and gradual increase of activity, and the accomplishment of personalised goals.

Instruments

Fatigue: The subscale fatigue severity from the Checklist Individual Strength (CIS) was used to measure the level of fatigue in our patients. It consists of eight items which are scored on a 7-point Likert scale. The sum score varies between 8, no fatigue, and 56, extremely severe fatigue. The cut-off score for severe fatigue used in this study was 35 (or higher). The CIS is a reliable and valid instrument for the assessment of fatigue in CFS patients (Vercoulen et al., 1994; Dittner et al., 2004). The Cronbach's alpha reliability coefficient for the fatigue severity subscale is 0.88 (Vercoulen et al., 1994).

Disability: The level of disability was measured with two instruments. Both instruments assess aspects of the effect of CFS on daily functioning and were used as primary outcome measures in the original trial of Knoop et al. (2008). The physical functioning subscale from the 36-item Short Form Health Survey (SF-36) was used to measure physical disability (Stewart et al., 1988). The scores on this scale range from 0, maximal limitations, to 100, no limitations at all. The Sickness Impact Profile (SIP) was used to assess overall impairment in eight different areas (Bergner et al., 1981). A sum score was computed using the subscales home management, ambulation, mobility, alertness behaviour, social interactions, sleep/rest, recreation, and work (Prins et al., 2001). Higher scores indicate more overall impairment.

Focus on symptoms: We used the somatic complaints subscale of the Symptom Checklist 90 (SCL-90) (Arindell & Ettema, 1986) to assess focusing on symptoms. Following Vercoulen et al. (1998), higher scores on this scale indicate a stronger focus on symptoms.

Perceived problems with activity: We used the activity subscale of the Checklist Individual Strength (CIS) to assess perceived problems with activity in our patients. The scale has 3 items which are scored on a 7-point Likert scale (e.g. "I don't do much during the day", "I have a low output in terms of activity"). The sum score on this scale varies between 3 and 21.

Higher scores on this scale indicate more problems with activity. The Cronbach's alpha reliability coefficient for this subscale of the CIS is 0.87 (Vercoulen et al., 1994).

Sense of control: The perceived level of control over fatigue was measured with the Self-Efficacy Scale (SES). This scale consists of five items (e.g. "I think that I can influence my fatigue", "I feel helpless against my fatigue"). Four of these items were scored on a 5-point and one item on a 4-point Likert scale. Higher scores on this scale indicate more sense of control over fatigue. The internal consistency of this scale ranges between .68 and .77 (Prins et al., 2001; de Vree et al., 2002).

Analyses

We conducted a multivariate general linear model (GLM) to test whether baseline scores of fatigue, disability, focusing on symptoms, perceived problems with activity, and sense of control differed between those patients who were excluded from our study due to missing data and those patients who were included. To correct for type I errors (i.e. incorrect rejection of true null hypotheses), we took only significant differences on the univariate tests into account when the multivariate test yielded significance as well.

Structural Equation modelling (SPSS Amos, version 17) was employed to test the hypothesised treatment models using the maximum likelihood setting. Change scores (second minus baseline assessment) were used for all variables except for treatment which was entered as dichotomous (0/1) variable (Wiborg et al., 2010). All tests were conducted twice, once with physical functioning (SF-36) and once with overall impairment (SIP), because both disability scales were used as primary outcome measures in the original trial (Knoop et al.; 2008).The threshold for statistical significance was set at $p \leq .05$.

We started with a simple model in which treatment caused a change in fatigue and disability. A significant effect on these variables guaranteed an effective intervention on the primary outcome measures. We then tested, one factor at a time, whether a change in focusing on symptoms, perceived problems with activity and sense of control over fatigue significantly mediated the effect of the intervention on fatigue and disability. Mediators of the treatment effect needed to be significantly associated with treatment as well as treatment outcome. Factors which did not meet this precondition were excluded from further analysis (Baron et

al., 1986; Frazier et al., 2004). The mean mediation effect was tested with bootstrap analyses in which the observed dataset was randomly resampled 1000 times to generate population parameters (Preacher & Hayes, 2004). Next, we integrated all significant mediators of the treatment effect into one model and optimised this model in a final step. A modification index (MI) of $\geq$ 4 was used as threshold for introducing new pathways when they were also meaningful from a theoretical point of view. To control for potential confounders, we also tested the final model with gender, age, and illness duration as cause for mediators and treatment outcome.

The fit of the models was tested following the recommendations of Buhi et al. (2007). We tested whether models actually fitted the data using the χ^2 statistics. Lower χ^2 values were preferred and p-values of $\geq$.05 indicated that the model did not have to be rejected. Due to limitations of the χ^2 statistics, we also report the comparative fit index (CFI) and the root mean square error of approximation (RMSEA). The CFI was used to show how much better the model fitted the data than a null model without common factors. The closer the CFI was to 1.00, the more superior the model was to the null model. Values of 0.95 or higher indicated a good fit. The RMSEA was used to indicate how well the model approached the data, assuming that there is no perfect model. Simpler models with fewer parameters are rewarded by this index. RMSEA values of $\leq$ 0.06 indicated a good fit of the model (Hu & Bentler, 1999). RMSEA values between > 0.06 and $\leq$ 0.10 indicated a fit of the model that was still acceptable (Weston & Gore, 2006). P-values of $\geq$.05 confirmed that the RMSEA was not significantly higher than 0.10.

RESULTS

Multivariate testing showed no significant differences on baseline assessment of fatigue, disability, focusing on symptoms, perceived problems with activity, and sense of control between those patients who were excluded due to missing data and those patients who were included (table 1). Univariate differences on these variables were therefore not further tested.

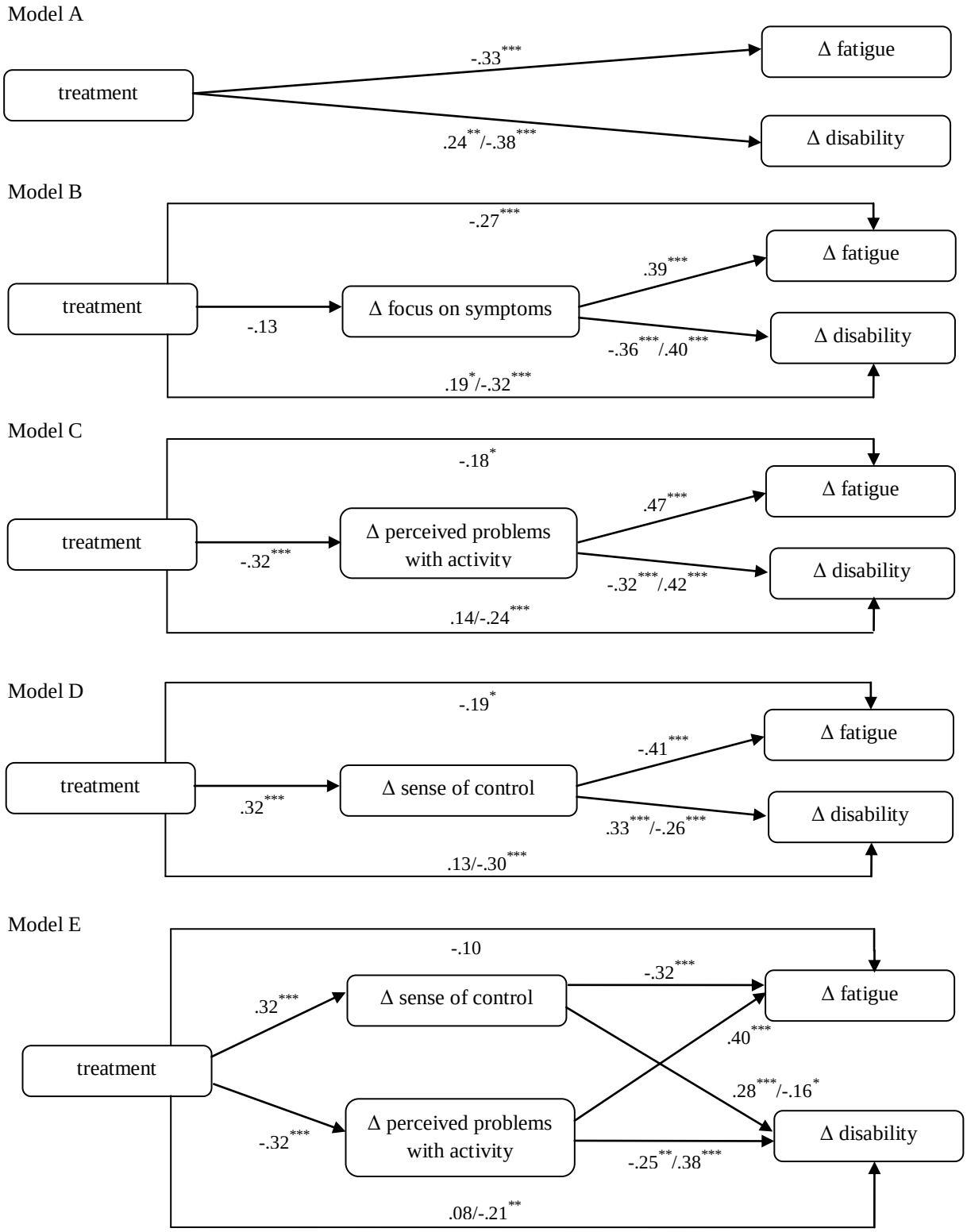
Table 1: Testing the differences on mean baseline scores (*SD*) due to exclusion.

	included	excluded	*F*	*p*
n (CBT)	139 (64)	30 (20)		
multivariate Wilks-Lambda	0.97		0.82	.560

In figures 2 and 3, we present the development of our treatment model. The fit of the different models is presented in table 2. All tests were conducted twice, once with physical functioning and once with overall impairment as disability measure. The test of model A confirmed that treatment significantly reduced the level of fatigue and disability in our selection of patients (figure 2). In models B-D, we tested one hypothesised mediator of the treatment effect at a time. The test of model B showed that treatment did not significantly affect the focus on symptoms in our patients. We therefore excluded this variable from further analysis. Testing models C and D revealed that a decrease in perceived problems with activity and an increase in sense of control over fatigue both significantly mediated the effect of our intervention (table 2).

Although the model fit increased with the introduction of these variables when compared with the simple treatment model, the model fit was still inadequate. In particular, all models had to be rejected according to the χ^2 statistics. Some CFI values indicated that their models were substantially better than a null model but the RMSEA showed that these models still did not approach the data well enough. We therefore integrated both significant mediators of the treatment effect into model E which resulted in a substantial increase in mediation effect sizes but not in model fit. In a final step, we optimised our treatment model by excluding non-significant pathways and introducing new conceptually meaningful pathways in accordance with the modification index (MI). The final model is depicted twice in figure 3, once for physical functioning and once for overall impairment.

Figure 2: Developing a model for cognitive behavioural interventions focusing on chronic fatigue syndrome including standardised effects (β) derived with structural equation modelling (N=139). Each model is tested with physical functioning (left effects) as well as overall impairment (right effects) as measure for disability.



Note. ***p≤.001. **p≤.01. *p≤.05.

Table 2: Testing the fit of the various models, including analyses of the mediation effects (N=139).

Model	χ^2 (*df*)	*p*	CFI	RMSEA	*p*	SME	*% total effect*	*p*
A[1]	53.2 (1)	≤.001	0.29	0.61	<.001			
A[2]	18.4 (1)	≤.001	0.67	0.36	<.001			
B[1]	37.8 (1)	≤.001	0.64	0.52	<.001			
B[2]	6.6 (1)	≤.010	0.94	0.20	≤.050			
C[1]	39.8 (1)	≤.001	0.68	0.53	≤.001	-.15[a]	45	≤.010
						.10[b]	42	≤.010
C[2]	5.1 (1)	≤.010	0.96	0.17	.051	-.13[c]	34	≤.010
D[1]	39.7 (1)	≤.001	0.66	0.53	≤.001	-.13[a]	39	≤.001
						.11[b]	46	≤.001
D[2]	11.1 (1)	≤.001	0.89	0.27	≤.010	-.08[c]	21	≤.001
E[1]	40.9 (2)	≤.001	0.76	0.38	≤.001	-.23[a]	70	≤.001
						.17[b]	71	≤.001
E[2]	12.3 (2)	≤.010	0.93	0.19	≤.010	-.17[c]	45	≤.001
F[1]	2.0 (2)	.360	1.00	0.01	.476	-.24[a]	73	≤.001
						.18[b]	75	≤.001
F[2]	4.7 (2)	.096	0.98	0.10	.175	-.17[c]	45	≤.001
F[1*]	4.4 (6)	.622	1.00	0.00	.783	-.24[a]	73	≤.001
						.16[b]	67	≤.001
F[2*]	7.2 (6)	.306	1.00	0.04	.510	-.16[c]	42	≤.001

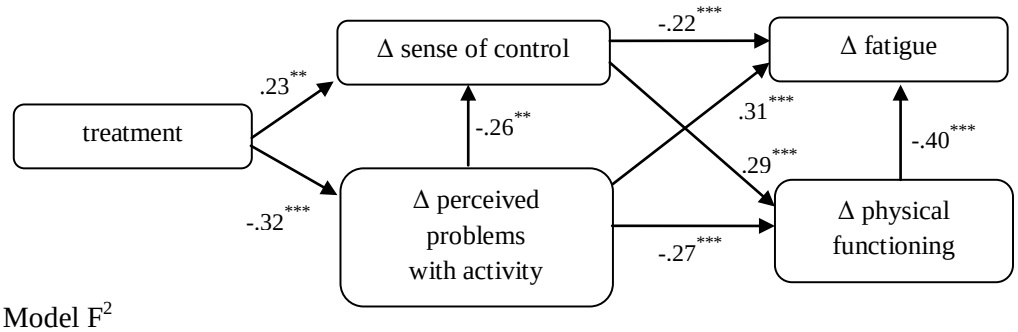
Note. [1] Model for physical functioning. [2] Model for overall impairment. CFI: comparative fit index. RMSEA: root mean square error of approximation. SME: standardised mediation effects of treatment on fatigue [a], physical functioning [b], and overall impairment [c]. Percentage total effect refers to the proportion of total treatment effect on treatment outcome that is explained by the mediators. [*] Controlling for the potential confounders gender, age, and illness duration.

In both models of figure 3, the pathway between treatment and changes in fatigue was deleted because it was no longer significant with the mediators in the model (73% of the total treatment effect on fatigue was explained by the mediators). The same accounted for the pathway between treatment and changes in physical functioning (the mediators explained 75% of the total treatment effect on physical functioning). In both models, a new pathway was introduced between changes in perceived problems with activity and changes in sense of control over fatigue. The modification index did not favour a direction for this effect (MI= 8.3 for both directions in both models). Both solutions were also identical in terms of model fit. We favoured a pathway from changes in perceived activity to changes in sense of control

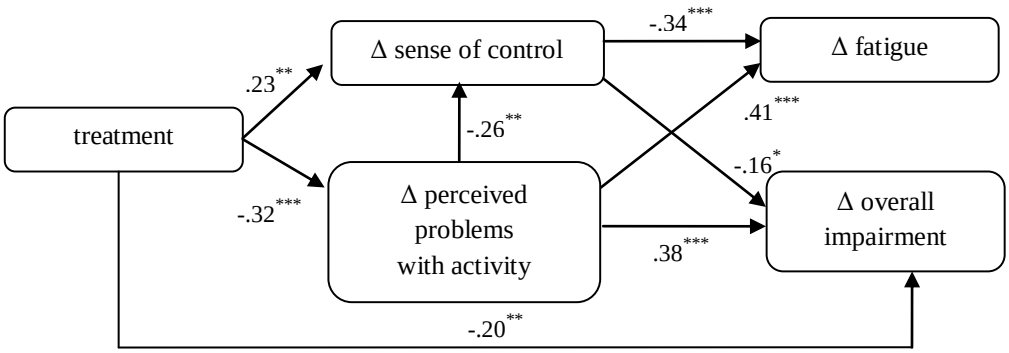
based on our understanding of CBT for CFS. In the physical functioning model, a pathway from changes in physical functioning to changes in fatigue was added for the same reason. This preference was in accordance with the modification index (MI= 22.9 as opposed to 18.2 for the opposite direction). Both solutions were identical in terms of model fit.

Figure 3: Testing the final optimised treatment model for physical functioning as well as overall impairment including the standardised effects (β) derived with structural equation modelling (N=139).

Model F[1]



Model F[2]



Note. ***p≤.001. **p≤.01. *p≤.05.

To control for potential confounders, we added gender, age, and illness duration to the model, hypothesising that these variables might influence mediators as well as treatment outcome. We were particularly interested in how robust our mediation effects would turn out to be under these circumstances. As shown in table 2, the mediation effects remained significant and largely unchanged. Interestingly, some fit indexes (in particular the RMSEA) profited from controlling for potential confounders. Both F models were accepted as the final treatment models.

DISCUSSION

In the present study, we developed the first treatment model in the context of CFS which evaluates the contribution of more than one significant mediator of the treatment effect. We found that the effect of our intervention on fatigue, the central feature of CFS, remained significant until we integrated changes in perceived problems with activity and sense of control over fatigue into one model. The introduction of a pathway between the two mediators further enhanced the model. These findings may suggest that both mediators intertwine to reduce the symptomatology of CFS patients.

Based on our understanding of CBT for CFS, we assumed that a perceived decrease in problems with activity might help to undermine the belief that the symptoms are uncontrollable and thereby facilitate a reduction in symptomatology. It is a major limitation of our study, though, that the mediators were not assessed while treatment was proceeding. This information would have contributed substantially to establishing causality among the factors of our model. This problem of temporality is also evident with respect to the outcome variables. We assumed that a reduction of reported physical dysfunction might precede a change in fatigue based on the prominent role of a graded activity program early in treatment (Bleijenberg et al., 2003). However, alternative models may also be plausible while fitting the data equally well.

Our findings are in line with a number of other studies which found that evidence-based interventions for CFS may need to change the perception and beliefs of their patients in order to be successful (Deale et al., 1998; Moss-Morris et al., 2005; Wiborg et al., 2010; 2011). These findings are also in accordance with a recent study about chronic fatigue in multiple sclerosis which showed that the effect of CBT was mediated by a change in the perception of fatigue (Knoop et al., 2011). Based on these findings, CBT as well as GET therapists may want to deemphasise the role of physiological processes when they introduce the treatment rationale of their intervention to patients. In addition, they may want to systematically facilitate and monitor changes in cognitive processes that seem to be vital to successful treatment of CFS. These modifications might help to further enhance the generally moderate effects of evidence-based interventions for patients with CFS.

Although all patients should profit from a change in illness perception, the group of pervasively passive patients may also need to get physically more active. This group is

characterised by an extremely low level of physical activity on almost all days. Such a pattern is particularly rare in healthy individuals and has led to an adaptation of the CBT for CFS manual introduced by Bleijenberg et al. (2003). The fact that the vast majority of CFS patients is relatively active might explain why increases in physical activity have not been found to play a role in the group as a whole (Wiborg et al., 2010). In future trials, the number of pervasively passive patients should be increased to conduct a separate test of the physical performance hypothesis for this subgroup.

In contrast to what we expected, we had to exclude the focus on symptoms because it was not significantly changed by treatment. Even though we used the somatic complaints subscale of the SCL-90 in accordance with Vercoulen et al. (1998) to operationalise the process of focusing on symptoms, other scales may reflect this construct more accurately. Examples of such scales are the Illness Perception Questionnaire (Moss-Morris et al., 2005) and an adaptation of the Pain Coping Inventory (Wiborg et al., 2011) in which patients are interrogated about their preoccupation with symptoms. Another promising strategy in this context is the experimental assessment of attentional biases for fatigue-related information (Knoop et al., 2010). Unfortunately, none of these instruments were available in the trial of Knoop et al. (2008).

There are further limitations to our study. We mentioned the problem of temporality due to simultaneous assessment of mediators and treatment outcome. This problem is particularly salient with respect to the relationship between changes in perceived problems with activity and fatigue severity because both scales stem from the same instrument (i.e. the Checklist Individual Strength). In addition, we assumed *a priori* that a change in all mediators should have the potential to affect all outcome variables. Although this idea was confirmed in models C and D, based on the model of Vercoulen et al. (1998) a link between changes in sense of control and disability should not have been introduced until the final optimisation of the treatment model. Furthermore, although we controlled the final model for gender, age and illness duration, other unmeasured variables may confound our mediation effects and thereby undermine the validity of our treatment model (Emsley et al., 2010). Finally, the validity of our findings might have also been affected by our compromise between "theory-driven" and "data-driven" techniques in the development of our treatment model.

In sum, a replication of our findings in prospective intervention studies is thus needed to validate our treatment model. This validation should be accomplished with studies that are primarily designed to examine treatment process. In such studies, change hypotheses can be generated beforehand based on the insights of the present study. Using alternative instruments for the assessment of focusing on fatigue and perceived problems with activity should thereby be considered. In addition, the process variables should be assessed repeatedly during treatment to enlighten the exact sequences of change and to help better understand the causality of the mutual relationships.

Although we deleted the direct effects of treatment on fatigue and physical functioning because they were no longer significant, the total treatment effect on outcome that was explained by our mediators did not exceed 75%. Additional mediators should therefore be added to the model. Besides the focus on symptoms, social support is a promising candidate, in particular in the context of overall impairment. Both, too little as well as too much support has been shown to contribute to the persistence of CFS (Prins et al., 2004). Less extreme scores on this variable may therefore be of potential value for patients who suffer from CFS. Finally, it should also be examined whether our low intensity cognitive behavioural intervention works through the same mechanisms as regular CBT for CFS, which has been shown to produce stronger effects than the low intensity intervention (Tummers et al., 2010).

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5

Implementing evidence-based practice for patients with chronic fatigue syndrome

Jan F Wiborg, Michel Wensing, Marcia Tummers, Hans Knoop & Gijs Bleijenberg

Submitted

ABSTRACT

The aim of our study was to explore whether community-based mental health care centres (MHCs) are able to implement and sustain cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS) with the help of an implementation manual for team leaders. We monitored the implementation data of three Dutch MHCs. Implementation success was defined as having included at least 40 CFS patients of which 30 or more completed post-treatment assessment and as having uncontrolled effect sizes within the statistical benchmark range of randomised controlled trials (RCTs) in the context of CBT for CFS. All MHCs included 40 or more patients with CFS of which more than 30 completed post-treatment assessment. Two MHCs received external support in addition to the implementation manual to achieve these results. These MHCs both implemented CBT for CFS for the first time, one in the context of a stepped care program for CFS. Two of three MHCs reached effect sizes similar to RCTs in terms of decreasing fatigue severity and physical disability. The MHC with the stepped care program had less favourable outcome data in the regular CBT condition with effect sizes that did not meet the range of the statistical benchmark. The findings of this study suggest that external support in addition to a standardised implementation manual helps MHCs to coordinate the initial implementation of CBT for CFS. After initial implementation, MHCs seem able to sustain CBT for CFS without additional support. Successive implementation of cognitive behavioural interventions should be considered in the context of stepped care for CFS.

INTRODUCTION

Patients with chronic fatigue syndrome (CFS) suffer from medically unexplained and severely disabling fatigue which lasts for at least six months (Fukuda et al., 1994). During the last two decades, cognitive behavioural therapy (CBT) for CFS has been developed and tested in specialised treatment settings (e.g. Sharp et al., 1996; Deale et al., 1997; Prins et al., 2001; Knoop et al., 2008; White et al., 2011). In CBT for CFS, dysfunctional illness beliefs are usually challenged through a gradual increase in activity and cognitive restructuring techniques. This strategy is effective in reducing fatigue and disabilities in CFS patients (Malouff et al., 2008; Price et al., 2008). Consequently, there is a growing interest in the dissemination of CBT for CFS outside specialised settings. For example, the Health Council of the Netherlands (2005) urged to implement CBT for CFS on a large national scale to treat an estimated number of 30.000-40.000 Dutch CFS patients.

Scheeres et al. (2006; 2008) examined the specific requirements for successful implementation of CBT for CFS outside specialised treatment settings. They approached a community-based mental health care centre (MHC) for their purpose and found that therapists needed specific training and supervision in addition to the CBT for CFS manual in order to treat patients effectively. Also, referrers and patients had to be informed regularly about the additional therapy offer so that treatment capacities could be exploited adequately. In addition, an optimised patient flow, which included the avoidance of prolonged waiting periods, was necessary to reduce unexpectedly high drop-out rates. A benchmark analysis (Scheeres et al., 2008) showed that the MHC was similarly effective in reducing fatigue and disabilities under these circumstances as randomised controlled trials (RCTs) in the context of CBT for CFS.

Based on this promising finding, Scheeres et al. (2006) wrote a manual in which they described their experiences with implementing CBT for CFS outside specialised settings. The main idea of this manual was that MHCs might be able to adopt CBT for CFS without additional help when they are adequately informed about the specific demands of the implementation. This could be of particular advantage for cost efficient dissemination of evidence-based practice for CFS on a large scale.

The aim of the present study was to examine whether MHCs are able to implement and sustain CBT for CFS with the help of the implementation manual introduced by Scheeres et

al. (2006). For this purpose, we evaluated three different implementation scenarios: new as well as sustained implementation of CBT as the only intervention for CFS, and new implementation of CBT in the context of a stepped care program for CFS. In stepped care for CFS, a low intensity variant of CBT for CFS can precede regular CBT. The low intensity intervention consists of written self-instructions and e-mail contact with a trained therapist (Knoop et al., 2008). There is evidence that stepped care for CFS is equally effective but more time efficient than regular CBT alone (Tummers et al., 2010).

METHODS

Setting

Our study was conducted at three Dutch MHCs. One was located in an urban region in the west of the Netherlands. The two other MHCs were located in rural areas, one in the east and one in the south of the Netherlands. All MHCs selected a team of cognitive behavioural therapists that was willing to participate in our study. The number of therapists who treated patients with CFS varied between seven at the eastern, two at the western, and four at the southern MHC. Each MHC also selected a team leader to coordinate the implementation of CBT for CFS.

All team leaders received the implementation manual of Scheeres et al. (2006), which contained specific information about the use of CBT for CFS outside specialised treatment settings. This information included recommendations about selection, training and supervision of cognitive behavioural therapists, activities to inform potential referrers and patients about the new treatment option, and optimising patient flow from initial referral to end of treatment, including routine assessment of fatigue and disabilities.

The eastern MHC sustained regular CBT for CFS from the study conducted by Scheeres et al. (2006; 2008). Therapists at this MHC received supervision in CBT for CFS once a month for one and a half hour. The western and the southern MHCs both implemented regular CBT for CFS for the first time. Therapists received a CBT for CFS manual, a four day training for therapists, and regular supervision twice a month for one and a half hour. The training and supervision of therapists was provided by members of our research team. Implementation progress was discussed with the team leaders at biannual research meetings.

The southern MHC also had a team of psychiatric nurses that delivered a low intensity intervention for CFS in the context of a stepped care program. Patients who were not improved after the low intensity intervention were referred to regular CBT. Patients who were not eligible for the low intensity intervention for some reason or who preferred face-to-face contact with a therapist could also start directly with regular CBT. In the present study, we focused on the data that were gathered during regular CBT for CFS. The effect of the low intensity intervention will be examined in the context of a RCT which is outside the scope of this study.

Patients

All patients were referred by a medical doctor with the diagnosis CFS which implied that patients were suffering at least six months from a severe and disabling fatigue in the absence of a medical explanation for the complaints (Fukuda et al., 1994; Reeves et al., 2003). We included patients with severe fatigue and disabilities at baseline assessment who were at least 18 years of age.

Measures

The subscale *fatigue severity* from the Checklist Individual Strength (CIS) was used to indicate the level of fatigue (Vercoulen et al., 1994; Dittner et al., 2004). This scale consists of eight items which are scored on a 7-point Likert scale. The sum score varies between 8, no fatigue, and 56, very severe fatigue. The cut-off score for severe fatigue was 35 (or higher). The level of disabilities was measured with the subscales *physical* and *social functioning* from the 36-item Short Form Health Survey (SF–36) (Stewart et al., 1988). The scores on both scales range from 0, maximal limitations, to 100, maximal functioning. The cut-off score for severe disabilities was 65 (or less) on physical or social functioning.

Data collection

We monitored the implementation data in collaboration with the MHCs who provided routinely collected and anonymised patient information on a regular basis to us. This information included the number of patients per stage of the patient flow (i.e. referral, start of

treatment, end of treatment) and the assessment of fatigue and disabilities prior and subsequent to treatment.

Analysis

Consensus was reached prior to the start of the study that at least 40 patients should be included per MHC and that at least 30 of these 40 patients should complete post-treatment assessment. In accordance with Scheeres et al. (2008), we determined the number of clinically improved patients with a reliable change index of >1.96 on the CIS fatigue severity, a fatigue severity score of $\leq$35 and a SF-36 physical functioning score of $\geq$65. We also followed the statistical benchmark procedure of Scheeres et al. (2008) to test whether treatment outcome in our MHCs was similar to the outcome of RCTs. This procedure included an uncontrolled pre-post benchmark effect size for fatigue severity and physical functioning which was calculated as ($M_{\text{baseline}} - M_{\text{post-treatment}}$) / pooled *SD*. MHCs that produced effect sizes within the 95% confidence interval of the statistical benchmark of Scheeres et al. (2008), were considered to be successful in generating effects similar to those found in RCTs. Our effect sizes were computed on the basis of intention to treat but patients who were still in treatment at the end of our study were excluded from the analyses. Missing data from patients who decided not to start with treatment or who were no longer in treatment and had not completed post-treatment assessment were imputed as last observation carried forward.

RESULTS

Implementation process

As described, we defined success in terms of the implementation process as 40 or more inclusions per MHC of which at least 30 completed post-treatment assessment. Each of the three MHCs fulfilled these criteria at the end of the implementation period (table 1). However, during this process, our monitoring data revealed referral problems at two MHCs and, in particular, alarming ratios of included patients in proportion to completed post-treatment assessments at all MHCs. Halfway through the implementation period, the eastern MHC had 43 inclusions and 8 completed post-treatment assessments, the western MHC had 21 inclusions and 5 post-treatment assessments, and the southern MHC had 16 inclusions and 1 post-treatment assessment.

Table 1: Implementation process data per MHC.

	Eastern MHC	*Western MHC*	*Southern MHC*
included	75	40	48
mean age (*SD*)	37.2 (11.6)	32.3 (10.8)	42.6 (10.8)
female	63 (84%)	30 (75%)	40 (83%)
treated	67	39	47
completed	43 (64%)	33 (85%)	32 (68%)
drop-out	15 (22%)	5 (13%)	5 (11%)
still in treatment	9 (13%)	1 (1%)	10 (21%)

Note. Percentages may not equal 100 because of rounding.

We discussed this issue at one of the biannual research meetings with all team leaders and agreed to provide external support in addition to the implementation manual to optimise the use of CBT for CFS. The additional support was provided during the second half of the implementation period by members of our research team to the team leaders and administrative employees of the western and the southern MHCs where CBT for CFS was newly implemented. We did not intervene in the sustaining process of the eastern MHC which already had received additional external support by members of our research team during the implementation study of Scheeres et al. (2006; 2008).

Our additional support included monthly feedback about the monitoring data for the team leaders of the western and the southern MHCs. This feedback contained an overview of the patient flow such as the number of included and treated patients, the average time patients waited for treatment, the average treatment time, and information about the use of post-treatment assessment. This information was interpreted by us in terms of implementation success (i.e. how many more inclusions and completers are needed and what is a tolerable drop-out rate under the given circumstances). We provided administrative employees with information about missing data. In some cases, we assisted in the assessment of fatigue and disabilities. We also provided administrative employees with information about potentially stagnating treatments (i.e. treatment periods of more than 6 months). At the western MHC, we supported the adoption of the monitoring system by one of the therapists due to structural problems at the level of the administrative employees.

In addition, we stimulated both team leaders to intensify their patient recruitment activities and to optimise the patient flow for CFS patients at their MHC in accordance with

the implementation manual. At the western MHC, we stimulated personal presence at meetings of general practitioners and publications in local newspapers. At the southern MHC, activities were stimulated that focused on motivating patients to continue with treatment after ineffective low intensity interventions for CFS. Only 10 of the 23 patients (43%) who were eligible to continue their treatment in the context of stepped care halfway through the implementation period actually started with regular CBT. We also stimulated team leaders to reduce prolonged waiting and treatment periods to avoid drop-out of patients before and during treatment whenever appropriate.

The western MHC had 19 inclusions and 28 post-treatment assessments in the period with external support as opposed to 21 inclusions and 5 post-treatment assessments in the period without external support. The southern MHC had 32 inclusions and 31 post-treatment assessments in the period with external support as opposed to 16 inclusions and 1 post-treatment assessment in the period without external support. The eastern MHC also improved their ratio of included patients in proportion to completed post-treatment assessments after the meeting where it was problematised. Here, 32 patients were included and 35 post-treatment assessments were completed after the meeting as opposed to 43 inclusions and 8 post-treatment assessments before the meeting.

At the end of our study, the team leaders of the western and southern MHC reported that the additional external support helped them to gain more insight into the progress of their implementation and at the same time helped everyone to keep focused and motivated during the implementation process. All team leaders appreciated the fact that they were able to determine how much external support was ultimately provided.

Treatment outcomes

The treatment outcome data per MHC are presented in table 2. Besides the number of clinically significant improved patients, we calculated uncontrolled effect sizes for fatigue severity and physical functioning. We defined success in terms of treatment outcome as effect sizes that were inside the range of the confidence intervals of the statistical benchmark introduced by Scheeres et al. (2008).

Table 2: Treatment outcome data per MHC.

	Eastern MHC	*Western MHC*	*Southern MHC*
intention to treat[*]	66	39	38
clinically sign. improved (%)	26 (39%)	26 (67%)	10 (26%)
mean Δ fatigue (*SD*)	-13.9 (15.6)	-24.0 (18.7)	-8.6 (13.4)
uncontrolled effect size	1.19	1.76	0.88
statistical benchmark[**]	0.97-1.89	0.97-1.89	0.97-1.89
mean Δ phys. functioning (*SD*)	14.8 (21.2)	29.9 (26.8)	10.3 (22.0)
uncontrolled effect size	0.65	1.23	0.43
statistical benchmark[**]	0.63-1.44	0.63-1.44	0.63-1.44
completers[***]	43	33	32
clinically sign. improved (%)	26 (60%)	26 (79%)	10 (31%)
mean Δ fatigue (*SD*)	-21.3 (14.7)	-28.4 (16.9)	-10.2 (14.0)
mean Δ phys. functioning (*SD*)	23.0 (22.3)	35.3 (25.6)	12.2 (23.5)

[*]Patients who were still in treatment were excluded. [**]95% confidence interval derived from Scheeres et al. 2008. [***]Patients who did not complete post-treatment assessment were excluded.

The eastern and the western MHC both had effect sizes that ranged within the 95% confidence intervals of the benchmark, indicating that they were successful in generating treatment effects similar to those found in RCTs. The effect sizes for regular CBT at the southern MHC were significantly lower than the effect sizes of the statistical benchmark. In total, forty-eight patients were included for regular CBT at the southern MHC. Fifty per cent (n=24) of the inclusions already had received a minimal intervention for CFS in the context of stepped care. Two of these patients were still in treatment at the end of the study. Four (18%) showed clinically significant improvement. The other 50% (n=24) of the inclusions had not received a low intensity intervention for CFS prior to regular CBT. Eight of these patients were still in treatment at the end of the study. Six (38%) showed clinically significant improvement.

DISCUSSION

The purpose of the present study was to examine whether MHCs are able to implement and sustain CBT for CFS with the help of the implementation manual introduced by Scheeres et al. (2006). Although all three MHCs fulfilled the success criteria in terms of the implementation process (i.e. at least 40 inclusions and 30 completers), the two new MHCs

both received additional implementation support by our research team. This support mainly included assistance for the team leaders in translating the implementation manual into practice and their administrative employees in processing the monitoring data into meaningful feedback for those involved in the implementation process.

Although our study was not primarily designed to test the effect of external support on implementation success, our findings suggest that we helped the MHCs to coordinate the initial implementation of CBT for CFS by responding to their need for more assistance. This would be in accordance with a notion of Fixsen et al. (2009), who stated that all professionals who participate in the implementation of evidence-based practice need supervision in order to be effective. Apparently, we have underestimated this need by limiting our supervision to the therapists in the first place. At the same time, we experienced the support that was based on the implementation manual in this study as substantially less time consuming than the support that was delivered in the implementation study of Scheeres et al. (2008) where no such manual existed.

Although the eastern MHC also had problems with the inclusion to completers ratio during the implementation process, our data suggest that MHCs are capable of sustaining CBT for CFS successfully without external support after initial implementation. It is vital to notice in this context that the eastern MHC did not express a need for more external support. In future implementations of CBT for CFS programs, it may be most appropriate based on our findings to adapt the level of additional support to the specific needs of the individual MHCs.

According to the statistical benchmark introduced by Scheeres et al. (2008), the effect sizes of the eastern and the western MHCs were similar to those found in RCTs. This result is another promising finding for future implementations of CBT for CFS outside specialised treatment settings. At the same time, the southern MHC had significantly lower effect sizes than the statistical benchmark. There are several explanations which may account for this finding. One possibility is that therapists at the southern MHC may have been less effective in treating CFS patients according to the evidence-based standard. A recent study in the context of manualised CBT for CFS showed that therapists inside specialised treatment settings do not affect treatment outcome (Cella et al., 2011). It would be interesting to examine whether the efficacy of therapists outside specialised settings might differ significantly and which characteristics might cause such a difference.

Another possible explanation is the fact that the southern MHC implemented more than one cognitive behavioural intervention at the same time in the context of a stepped care program for CFS. None of the cognitive behavioural therapists were specifically trained for face-to-face contact with patients who already had received an ineffective low intensity intervention. This fact may have biased treatment outcome in disadvantage of the southern MHC. Although the number of patients was too small to test these differences statistically, our clinically significant improvement rates indicate that regular CBT for patients who had received the low intensity intervention may have been less effective than regular CBT for patients who had not received the low intensity intervention. Based on these findings, we would discourage implementation of more than one intervention for CFS at a time. We recommend to start with regular CBT which can be complemented with the low intensity intervention as soon as the initial implementation of regular CBT has been accomplished successfully.

Our conclusions are based on the assumption that the MHCs which participated in our study are exemplary for the implementation situation of other MHCs. Due to the heterogeneity of community-based mental health care, our findings may not fit seamlessly into other settings in and outside the Netherlands. Although we paid attention to factors which may be relevant for future implementations in our selection of MHCs (e.g. rural and urban regions are represented as well as different implementation scenarios), future research will have to demonstrate how well our findings generalise to these settings.

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6

Therapist effects and the dissemination of cognitive behaviour therapy for chronic fatigue syndrome in community-based mental health care

Jan F Wiborg, Hans Knoop, Michel Wensing & Gijs Bleijenberg
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ABSTRACT

The purpose of the present study was to explore the role of the therapist in the dissemination of manualised cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS) outside specialised treatment settings. We used the routinely collected outcome data of three community-based mental health care centres (MHCs) which implemented and sustained CBT for CFS during the course of the study. Ten therapists, who all received the same training in CBT for CFS, and 103 patients with CFS were included. Random effects modelling revealed a significant difference in mean post-treatment fatigue between therapists. The effect of the therapist accounted for 21% of the total variance in post-treatment fatigue in our sample. This effect could be explained by the therapists' attitude towards working with evidence-based treatment manuals as well as by the MHC where CBT for CFS was delivered. The context in which CBT for CFS is delivered may play an important role in the accomplishment of established therapy effects outside specialised treatment settings. Due to the small sample size of MHCs and the different implementation scenarios in which they were engaged, our findings should be interpreted as preliminary results which are in need for replication.

INTRODUCTION

The evolution of cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS) in specialised treatment units has led to a multitude of randomised controlled trials during the past fifteen years (e.g. Sharpe et al., 1996; Deale et al., 1997; Prins et al., 2001; Stulemeijer et al., 2005; Knoop et al., 2008; White et al., 2011). These trials generally showed that CBT is an effective treatment for the severe and disabling fatigue that is central to the suffering of CFS patients (Malouff et al., 2008; Price et al., 2008).

Several publications have recently been devoted to factors that may explain treatment outcome in CBT for CFS (Wiborg et al., 2010; Knoop et al., 2010; Wiborg et al., 2011; Cella et al., 2011). Most of these studies focused on changes in illness-specific behaviours and beliefs of the patient. In the present study, we explored the role of the context in which patients receive manualised CBT for CFS focusing on the effect of the therapist outside specialised treatment settings.

The individual therapist has received considerable attention in the endeavour to understand treatment outcomes in psychotherapy research (e.g. Luborsky et al., 1985; Lambert et al., 1989; Okiishi et al., 2003; Kim et al., 2006; Lutz et al., 2007; Cella et al., 2011). In general, the variance in treatment outcome that can be explained by the therapist tends to vary substantially across studies. While some studies have found explained variance estimates of up to 50%, others failed to demonstrate a significant therapist effect (Crits-Christoph et al., 1991). For example, Cella et al. (2011) recently found that 0% of the variance in post-treatment fatigue of a specialised CFS unit could be explained by the therapist. They attributed this finding to the fact that their therapists were equally well trained in manualised CBT for CFS.

However, depending on the context, therapists can also differ on other relevant characteristics than the amount of training in a manualised therapy approach. Addis and Krasnow (2000) showed that the attitude towards treatment manuals varies among therapists. This variation may affect treatment outcome in manualised therapies. Yet, less favourable attitudes towards treatment manuals were found outside specialised academic treatment settings and may therefore only affect outcomes outside such settings.

There is thus good reason to assume that the therapists of the specialised treatment unit examined by Cella et al. (2011) were generally positive about the use of treatment manuals,

with little variation downward. Outside specialised settings this may be fundamentally different, with vital consequences for the dissemination and use of manualised therapies.

In the present study, we were interested in whether therapists of community-based mental health care centres (MHCs), who received the same training in manualised CBT for CFS, contribute to the variation in post-treatment fatigue. We were further interested in whether these hypothesised variations in therapist efficacy can be explained by the therapists' attitude towards working with evidence-based treatment manuals as suggested by Addis et al. (1999; 2000).

METHODS

Design

We conducted an observational prospective study using the routine outcome data of three Dutch MHCs. All MHCs participated in a study about the implementation of CBT for CFS. One MHC sustained CBT for CFS from a pilot implementation (Scheeres et al., 2008). The two other MHCs implemented CBT for CFS during the course of this study. In one of these MHCs, the efficacy of a minimal intervention for CFS was tested simultaneously. As a result, some patients were referred to CBT after the minimal intervention. Data were gathered between 2008 and 2011 and included fatigue severity scores prior and subsequent to CBT for CFS and the therapists' attitude towards treatment manuals before patients were treated in the context of this study.

All therapists were trained and supervised in CBT for CFS by members of our research team. We analysed the data of therapists who treated at least three CFS patients including post-treatment assessment. Patients were referred by a medical doctor with the diagnosis CFS which implied that patients were suffering at least six months from a severe and disabling fatigue in the absence of a medical explanation for the complaints (Fukuda et al., 1994; Reeves et al., 2003). Patients who had fatigue scores below the cut-off level for severe fatigue at pre-treatment assessment as described beneath or who did not complete post-treatment assessment were excluded from this study. In total, 10 therapists and 103 patients were included. CBT for CFS was based on the treatment manual described by Bleijenberg et al. (2003) and Knoop and Bleijenberg (2010) and included goal setting, fixed sleep wake cycles,

changing the focus on bodily symptoms, a systematic challenge of fatigue-related beliefs, regulation and gradual increase of activity, and the accomplishment of personalised goals.

Instruments

The subscale *fatigue severity* from the Checklist Individual Strength (CIS) was used to indicate the level of fatigue experienced by patients (Vercoulen et al., 1994; Dittner et al., 2004). The scale consists of eight items which are scored on a 7-point Likert scale. The sum score varies between 8, no fatigue, and 56, very severe fatigue. The cut-off score for severe fatigue was 35. The internal consistency of the fatigue severity scale has been found to be good ($\alpha = .88$) (Vercoulen et al., 1994).

Therapists' attitude towards working with evidence-based treatment manuals was assessed with the survey questionnaire introduced by Addis et al. (2000) which was translated into Dutch for this purpose. The questionnaire consists of 17 items which load on two factors. The factor *negative process* reflects the idea that treatment manuals pose a threat to the freedom and flexibility of the therapist. The factor *positive outcome* addresses the idea that treatment manuals can enhance therapeutic results. The internal consistency of these factors has been found to be $\alpha = .93$ for negative process and $\alpha = .80$ for positive outcome (Addis et al., 2000).

Data analysis

We computed a series of multi-level random effects models using the lme4 library in *R* (Bates, 2010). The statistical significance of our effects was tested with 95% profile deviance confidence intervals (CI) using maximum likelihood fits. A confidence interval that did not include zero indicated statistical significance. Undefined lower bounds were interpreted as zero. At first, we computed a baseline model with post-treatment fatigue scores as dependent variable and therapist effect as random factor. An intra-class correlation coefficient (ICC) was computed as ratio of the therapist variance to the total variance. Next, we added both subscales of the therapists' attitude towards treatment manuals as fixed factor to the baseline model. Since therapists were delivering treatment at different MHCs, we also computed a model in which the treatment setting was added as fixed factor to the baseline model. We computed dichotomous dummy variables for this purpose. MHC I was used as reference

category in the dummy coding process (this MHC sustained CBT for CFS from an earlier implementation). All models were controlled for pre-treatment fatigue.

RESULTS

An overview of the distribution of patients and therapists among MHCs is presented in table 1, including therapist attitude and mean fatigue scores per therapist at pre-treatment and post-treatment assessment.

Table 1: The distribution of patients and therapists among community-based mental health care centres (MHCs), including therapist attitude and mean fatigue scores per therapist at pre-treatment and post-treatment assessment.

therapist and setting	*number of patients*	*mean pre-treatment fatigue (SD)*	*mean post-treatment fatigue (SD)*	*therapist attitude*	
				neg. process	*pos. outcome*
MHC I	40	50.6 (4.4)	30.0 (14.7)	21.9 (1.2)	32.0 (6.8)
1	8	49.4 (3.6)	37.5 (14.2)	23	26
2	4	51.8 (2.2)	31.5 (15.0)	21	40
3	9	49.0 (5.2)	20.0 (11.9)	20	24
4	11	52.5 (3.0)	31.6 (16.7)	22	40
5	8	50.6 (6.0)	30.6 (12.3)	23	32
MHC II	30	50.3 (6.1)	39.3 (12.7)	27.5 (0.5)	42.6 (5.0)
1	11	52.2 (6.1)	46.1 (7.6)	27	40
2	4	47.0 (8.8)	41.8 (10.7)	27	33
3	15	49.7 (5.2)	33.7 (13.9)	28	47
MHC III	33	51.0 (5.6)	22.7 (16.1)	22.5 (0.5)	38.5 (0.5)
1	16	53.0 (3.5)	22.8 (16.1)	22	39
2	17	49.2 (6.6)	22.5 (16.5)	23	38
total	103	50.7 (5.2)	30.4 (15.9)	23.7 (2.6)	37.2 (6.7)

Our baseline model revealed that there was a significant effect of the therapist on treatment outcome (variance component estimate = 53.0; CI: 10.3, 164.7). The ICC equalled .21 which indicated that 21% of the variance in post-treatment fatigue could be explained by the individual therapist (correcting for pre-treatment fatigue). Next, we added both attitude subscales to the baseline model. The variance component estimate for the therapist effect decreased from 53.0 to 21.8 (CI: 0.0, 63.3). The variance component estimates for *negative process* and *positive outcome* were 2.7 (CI: 0.9, 4.5) and -0.4 (CI: -1.0, 0.3) respectively, indicating that *negative process* was a significant predictor of the model.

In the final model, in which the treatment setting was added to the baseline model, the variance component estimate for the therapist effect dropped from 53.0 to 16.4 (CI: 0.0, 49.5). The variance component estimates for MHCs II and III were 9.7 (CI: 1.6, 18.0) and -7.4 (CI: -15.9, 1.1) respectively, indicating that MHC II (i.e. the MHC were the minimal intervention was implemented simultaneously) was the least effective in reducing fatigue in the regular CBT condition. In both models, the 95% confidence interval included zero which indicates that the therapist effect was no longer significant when either attitude or treatment setting were added to the baseline model. However, the confidence intervals of all models were large and overlapped each other.

DISCUSSION

In the present study, we explored the role of the context on treatment outcome in manualised CBT for CFS outside specialised treatment settings. We found that equally well trained therapists produce different outcomes. The effect of the therapist accounted for 21% of the total variance in post-treatment fatigue in our sample. This finding differs from the results of a recent publication by Cella et al. (2011) in which no therapist effect on treatment outcome was found following CBT in a specialised CFS unit. Our finding is in line, however, with the explained variance estimates reported in a meta-analysis by Crits-Christoph et al. (1991) which ranged between 0% and 50%.

In additional, we found that there was a substantial decrease in therapist effect when both attitude subscales were added to the model. In particular, a stronger belief that treatment manuals threaten the freedom and flexibility of therapists seems to be related to less effective treatments. To our knowledge, this study is the first one to link the attitude of therapists towards evidence-based treatment manuals to the efficacy of manualised therapy approaches.

Our analyses also revealed that the setting where therapists delivered CBT for CFS might as well account for the differences in therapist efficacy. An inspection of table 1 reveals that the scores on *negative process* and post-treatment fatigue are in fact mainly consistent with the setting where CBT for CFS was delivered. This finding may indicate an interplay between therapists and the setting in which they are employed. Treatment settings may, for example, facilitate certain beliefs about the use of treatment manuals in therapists or attract therapists who feel comfortable with the prevailing attitude of a given setting. Some settings may

therefore be less suitable for the dissemination of manualised therapies than others which might be reflected by the attitude of their therapists towards treatment manuals. However, negative beliefs about manualised therapies may also be receptive to change which could be induced through specific interventions that are delivered by external experts (Addis et al., 1999).

A major limitation of our study is that all MHCs were engaged in different implementation scenarios during the course of our study which may have affected treatment outcome. While two MHCs implemented CBT for CFS, one sustained it from an earlier implementation study. More experience in CBT for CFS might, for example, produce more favourable treatment outcomes. However, the MHC with the most favourable results was not the one that sustained CBT for CFS. In addition, the therapists of one MHC were confronted with patients who had already received an ineffective minimal intervention for CFS. This MHC had the least favourable outcomes. There was a trend at this MHC which suggests that treatment for patients who did not receive the minimal intervention might have been more effective than regular CBT following the low intensity intervention. Since we conducted an explorative study with the routinely collected outcome data of an implementation study, we were also not able to allocate patients randomly to the therapists which may have biased treatment outcome as well. Although we corrected for fatigue severity at baseline assessment, comorbidity may have complicated the caseload of some therapists more than that of others for example.

Representative data from routine clinical practice of CBT for CFS are scarce (Scheeres et al., 2008). This is particularly true for data being collected outside the context of specialised treatment settings. Understanding which factors may facilitate or impede established treatment effects in these settings is a major challenge for the dissemination of evidence-based interventions. Our study contributed to this endeavour with preliminary findings suggesting that the context where CBT for CFS is delivered may play an important role. Replication of our findings with a greater sample of MHCs is needed to show that these findings are not exclusively a consequence of the implementation scenario.

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7

Being homebound with chronic fatigue syndrome: A multidimensional comparison with outpatients

Jan F Wiborg, Sieberen van der Werf , Judith B Prins & Gijs Bleijenberg

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ABSTRACT

Many patients with chronic fatigue syndrome (CFS) seem to experience periods in which they are bound to home due to their symptomatology. Despite the ever growing body of knowledge about CFS, little is known about patients who feel no longer able to leave their house. The purpose of the present study was to examine whether homebound patients differ from other CFS patients on illness specific characteristics. Besides experiencing more impairment in daily functioning than participants of an outpatient intervention study, homebound patients were characterised by extremely high levels of daily fatigue, predominant somatic attributions and pervasively passive activity patterns. The course of symptomatology was similarly stable in both groups. Our findings suggest that homebound patients form a distinct subgroup of CFS patients who might profit from a treatment approach which is tailored to their specific needs. The exploratory nature of this first systematic investigation of homebound CFS patients is stressed and suggestions for future research are made.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterised by severe and disabling fatigue which persists at least six months and which is not the result of a medical condition (Fukuda et al., 1994). CFS can dominate the life of patients to such a degree that they feel no longer able to leave their house any more. According to surveys held by patient organisations, many patients with CFS seem to have experienced a period in which they were bound to their homes due to their symptomatology (e.g. Action for M.E., 2001). Unfortunately, virtually all scientific effort has been concentrated on CFS patients who were able to visit outpatient treatment settings. Thus, little is known about the illness specific characteristics of homebound CFS patients. More insight into these characteristics will enhance the understanding of the complex nature of CFS and may also contribute to the development of specifically tailored treatment approaches.

The purpose of the present study was to determine whether homebound patients differ from other CFS patients on illness specific characteristics. For this purpose, we compared a group of homebound patients with the natural course condition of an outpatient intervention study, previously conducted to test the effect of cognitive behaviour therapy (CBT) for CFS (Prins et al., 2001). The two groups were compared on multiple illness specific dimensions, validated for the clinical evaluation of patients with medically unexplained fatigue (Vercoulen et al., 1994). Besides the assessment of fatigue, impairment and additional complaints such as concentration problems, unrefreshing sleep and the deterioration in psychological wellbeing, those factors were assessed which have been shown to inflate and prolong symptomatology in CFS (Vercoulen et al., 1994; 1998). These perpetuating factors have received much attention, both in research and cognitive behaviour therapy for CFS (Prins et al., 2006). Prominent factors are physical inactivity, caused by the idea that the complaints are due to a somatic cause, and an experienced lack of control over symptoms. We hypothesised that the scores on these factors are more problematic in homebound patients than in outpatients, leading to more severe fatigue and impairment.

Earlier research has shown that spontaneous recovery in CFS is rare (for a systematic review see Cairns & Hotopf, 2005). No specific findings exist about the course of CFS in homebound patients. We therefore reassessed the severity of fatigue and impairment at one

year follow-up and tested whether the course of symptomatology in homebound patients differs from that of outpatients.

METHODS

Design

A Dutch patient organisation was asked to recruit CFS patients among its members who felt bound to their home. In order to participate, these members had to be between 18 and 60 years of age, had to meet the CDC criteria for CFS (Fukuda, 1994) and should not have participated in research on CFS before. Eighteen members fulfilled these criteria and were visited twice at home during a period of two weeks to complete baseline assessment. To prevent attrition among homebound patients, a limited test battery was used at follow-up assessment 12 months later. Fifteen homebound patients were able to complete follow-up assessment.

As reference group, we chose the natural course condition of a multi-centre randomised controlled trial, previously conducted by Prins et al. (2001) to test the effect of CBT on CFS. These 88 patients differed from the group of homebound patients in that they were able to participate in an outpatient treatment study despite of their symptomatology. In this trial, follow-up assessment took place 14 months after baseline assessment. Seventy-nine of the 88 patients completed follow-up assessment.

Assessment

Checklist Individual Strength: We used subscales of the Checklist Individual Strength (CIS) to assess fatigue severity and concentration problems. Higher scores indicate more severe fatigue and problems with concentration. The CIS is a reliable and valid instrument for multidimensional assessment of fatigue in CFS (Vercoulen et al., 1994; Dittner et al., 2004).

Daily observed fatigue: Patients were asked to rate the intensity of fatigue four times a day from 0 (no fatigue) to 4 (intense fatigue). The daily sum score was averaged across a period of two weeks (Vercoulen et al., 1996a). This score was used to compare fatigue levels at baseline because daily assessment of fatigue is less prone to a ceiling effect than single assessment of fatigue.

Sickness Impact Profile: Several subscales of the Sickness Impact Profile (SIP; Bergner et al., 1981) were used to measure impairment in different areas of functioning due to health problems. We were interested in the subscales home management, ambulation, mobility, alertness behaviour, social interactions, and sleep. Higher weighted scores indicate more impairment on these scales.

Karnofsky scale: The Karnofsky performance status scale (O'Dell et al., 1995) is a descriptive, ordinal scale. An independent clinical psychologist rates patient's level of daily functioning at 10-point intervals from 0 to 100. Lower ratings indicate more impairment in daily functioning.

Symptom Checklist: The Dutch version of the Symptom Checklist 90 (SCL; Arindell & Ettema, 1986) was used to assess psychological wellbeing. We were interested in the subscales anxiety, agoraphobia, depression, interpersonal sensitivity, somatisation, and sleep. Higher scores indicate more problems in these areas.

Actometer: Actigraphy was used to assess the level of physical activity. The Actometer is a motion-sensing device which is worn around the ankle during a period of two consecutive weeks. A mean score was computed to indicate the average daily level of physical activity, with higher scores indicating more physical activity. The Actometer has been shown to be a reliable and valid instrument for the assessment of physical activity in CFS (van der Werf et al., 2000).

Causal Attribution List: Attribution of CFS related symptoms was assessed with the Causal Attribution List (CAL). Somatic as well as non-somatic attributions were assessed on a 4-point Likert scale with 5 items per subscale. The mean norm score for CFS patients on somatic attributions is 14.0 (SD = 2.6) and 9.1 (SD = 2.4) on non-somatic attributions (de Vree et al., 2002), with higher scores indicating a stronger tendency to attribute symptoms to a certain cause. The internal consistency of the CAL ranges between .71 and .77 (Vercoulen et al., 1996b; Prins et al., 2001; de Vree et al., 2002).

Self-efficacy scale: Sense of control over fatigue was measured with the Self-Efficacy Scale (SES). This scale consists of five items. Four of these items were scored on a 5-point and one item on a 4-point Likert scale. Higher scores on the SES reflect more sense of control over symptoms. The mean norm score for CFS patients is 15.6 (*SD* = 3.4) and the internal consistency ranges between .68 and .77 (Prins et al., 2001; de Vree et al., 2002).

Statistical analysis

To avoid bias due to considerable differences in group size (i.e. 18 vs. 88), we selected the 28 patients of the natural course condition who scored within the same range as the homebound patients on age, gender and illness duration (i.e. between 27 and 56 years of age, female, with an illness duration between 4 and 32 years). Twenty-five of these 28 patients completed follow-up assessment.

Not all variables were normally distributed. Therefore, Mann-Whitney's non-parametric test was used to analyse differences between the groups. At first, we tested the differences in age and illness duration to assure that differences on the main outcome measures were not simply due to differences on these variables. Then, we tested the median differences on the main outcome measures at baseline assessment. Finally, we examined the median differences in change scores (follow-up versus baseline) on fatigue and impairment. The p-value for statistical significance has been set at $p < .05$. Due to the exploratory nature of the study, no formal correction for a type I error has been applied.

RESULTS

In table 1, the baseline differences between homebound patients and outpatients are shown. While the group of homebound patients did not differ significantly from the selection of outpatients in age, illness duration, and education, none of the homebound patients held a paid occupation, which was significantly less employment than was found in the selection of outpatients. The group of homebound patients also differed from the selection of outpatients on the three dimensions fatigue, daily functioning, and physical activity. All scale differences on these dimensions were significant to the detriment of the homebound patients.

Table 1: Testing differences in median baseline scores (range) between homebound patients and the selection of outpatients using Mann-Whitney's test

	homebound (n = 18)	selection outpatients (n = 28)	z	P
patient characteristics				
age in years	41.5 (27-56)	45 (27-56)	-0.79	.430
female	18 (100%)	28 (100%)	*n.a.*	*n.a.*
illness duration in years	10.0 (4-32)	7.5 (5-25)	-0.39	.700
paid occupation	0 (0%)	8 (28%)	*n.a.*	.015[a]
education[b]	4 (2-7)	4.5 (1-7)	-0.20	.845
psychological wellbeing				
SCL anxiety	15 (3-30)	14 (9-30)	-0.20	.839
SCL agoraphobia	7 (7-21)	8 (7-18)	-1.22	.222
SCL depression	26.5 (20-51)	28 (16-59)	-0.78	.436
SCL sensitivity	20 (18-41)	24 (19-43)	-2.04	.041
SCL somatisation	33 (23-52)	29 (14-45)	-2.03	.042
fatigue				
daily observed fatigue	14.1 (8.6-15.6)[c]	7.3 (0.4-13.2)[d]	-4.77	.000
daily functioning				
SIP home management	309 (54-498)	216 (54-421)	-2.29	.022
SIP ambulation	231.5 (0-678)	137 (0-315)	-2.85	.004
SIP mobility	336.5 (86-457)	127.5 (0-585)	-4.35	.000
Karnofsky scale	50 (40-70)[c]	70 (60-90)[c]	-5.28	.000
concentration				
SIP alertness behaviour	309.5 (0-687)	403.5 (0-777)	-1.35	.176
CIS concentration	24 (5-35)	29 (5-35)	-2.01	.044
social functioning				
SIP social interactions	235.5 (44-683)	325.5 (123-696)	-0.98	.327
sleep				
SCL sleep	7.5 (3-15)	7 (3-13)	-0.82	.414
SIP sleep	144 (83-499)	173.5 (49-395)	-0.66	.512
hours sleep at night	7 (3-13)	8.5 (5-12)	-1.16	.248
hours sleep at daytime	1 (0-6)	1 (0-4)	-0.35	.972
physical activity				
actigraphy	28.5 (5-46)	60 (30-97)	-5.11	.000
causal attributions				
CAL somatic	16.5 (9-20)	14.5 (10-18)	-2.62	.009
CAL non-somatic	10.5 (4-14)	9 (5-14)	-0.35	.725
sense of control				
SES	14 (6-21)	13.5 (10-20)	-0.21	.837

Note. [a] Fisher's exact test. [b]Higher scores indicate a higher level of education.
[c]One patient missing. [d]Three patients missing.

No significant differences were found on the dimensions social functioning, sleep and sense of control. The results for the dimensions psychological wellbeing, concentration, and causal attributions were mixed. While the two groups did not differ on most scales of the dimension psychological wellbeing, the median scores on interpersonal sensitivity and somatisation were significantly different between the two groups. According to the CIS concentration, the two groups also differed significantly on the dimension concentration but this finding was not supported by the SIP alertness behaviour. Finally, homebound patients attributed their symptoms significantly more to a somatic cause than the selection of outpatients. A significant difference on non-somatic attributions was not found.

The differences in change scores between the group of homebound patients and the selection of outpatients are presented in table 2. All reassessed scales indicate that the change from baseline to follow-up was not significantly different between the two groups.

Table 2: Testing differences in median change scores (range) between homebound patients and the selection of outpatients using Mann-Whitney's test

	homebound (n = 15)	selection outpatients (n = 25)	z	P
fatigue				
Δ CIS fatigue severity	0 (-21–12)	-2 (-37–7)	-0.53	.593
daily functioning				
Δ SIP home management	0 (-208–177)	0 (-202–154)	-0.56	.576
Δ SIP ambulation	-27 (-284–490)	-1 (-213–140)	-0.25	.801
Δ SIP mobility	-48 (-223–376)	0 (-438–170)	-0.59	.556
concentration				
Δ SIP alertness behaviour	0 (-180–219)	-55 (-299–153)	-1.58	.114
Δ CIS concentration	-2 (-9–9)	0 (-14–15)	-0.04	.966
social functioning				
Δ SIP social interactions	0 (-363–264)	-49 (-366–221)	-1.31	.189
sleep				
Δ SIP sleep	0 (-248–107)	-60 (-346–70)	-1.08	.280

DISCUSSION

Our findings suggest that homebound patients differ from other patients with CFS in a number of ways. At first, homebound patients were less likely to hold a paid occupation and experienced more impairment in daily functioning. This finding conceptually supports the

notion of being bound to home. Second, homebound patients experienced considerably higher levels of daily fatigue and were considerably less physically active. In fact, two thirds of their daily fatigue scores and half of their Actometer scores were not at all present in the reference group and all homebound patients were characterised by a pervasively passive activity pattern with an extremely low level of physical activity on almost all days (van der Werf et al., 2000). Furthermore, homebound patients were more prone to attribute their symptoms to a somatic cause than outpatients. Although homebound patients experienced considerably more fatigue and impairment, they did not report more change in symptomatology during the follow-up period than outpatients. In fact, many median change scores were equal to zero.

On the other hand, homebound patients did not feel socially more impaired or experienced less sense of control over their symptoms than outpatients. They were also not psychologically more distressed. At first sight, these latter findings may seem contradictory. One would assume that patients who are bound to home due to their symptomatology should also experience more distress and less sense of control over their symptoms. However, an extremely high level of daily fatigue in combination with a predominant belief in a somatic cause (while no somatic cure is available), might have urged these patients to withdraw from virtually any activity to exercise at least some control over their fatigue. While this way of adapting to the condition might have resulted in an increase in sense of control and a decrease in psychological distress, it could have also bound these patients to their homes and made them dependent on the help of others.

Besides resulting in serious impairment, this hypothesised way of adapting to the condition may also seriously complicate the delivery of treatment as any belief in the possibility to change might have been diminished in these patients. In addition, the predominant somatic attributions may cause a general reluctance towards psychological interventions. As a consequence, simply offering a home variant of treatment might be insufficient to reach these patients. In fact, although all of the participating homebound patients remained homebound at follow-up assessment none accepted our offer to follow CBT for CFS at home. When tailoring specific interventions for homebound patients, it should therefore be considered to facilitate a belief in the possibility to change in these patients as well as to increase the acceptability of psychological interventions to accomplish change. Furthermore, the social environment of homebound patients should actively be involved in

the treatment because others may unwittingly contribute to the persistence of the condition by taking over too many activities of the patient.

The number of homebound patients with CFS available for participation in our study was smaller than expected. As a consequence, the sample size of homebound patients remained restricted. Although we were able to detect a meaningful pattern of substantial differences which should allow for the discrimination of homebound CFS patients, the nature of this first systematic investigation of homebound CFS patients should be understood as being primarily exploratory. Our findings should therefore be cross-validated by future research. Furthermore, our adaptation hypothesis can be tested by following patients "at risk" of becoming bound to home. According to our findings, such patients are characterised by extremely high levels of daily fatigue, predominant somatic attributions and pervasively passive activity patterns. Finally, our suggestions for a treatment approach which is specifically tailored to the situation of homebound CFS patients can be further elaborated and tested in prospective treatment studies.

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8

General Discussion

In the preceding six chapters, new insights were gained about the mechanisms of successful change and the implementation of cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS). In this final chapter, the scientific and clinical implications of these new insights are discussed in more detail.

UNDERSTANDING EVIDENCE-BASED PRACTICE FOR CFS

A recent meta-analysis (Bronwyn et al., 2011) showed that CBT and graded exercise therapy (GET) are both moderately effective interventions for the treatment of CFS. This meta-analysis replicated earlier findings of systematic reviews about the treatment of CFS (Edmonds et al., 2004; Chambers et al. 2006 , Price et al., 2008; Malouff et al., 2008). In contrast to the extensive research literature on *whether* CBT and GET work, few empirical studies have raised the question *how* these interventions generate their effects. Different models have been proposed to explain how CBT and GET for CFS may work but none of them has been tested empirically. As a consequence, we do not know why patients profit from evidence-based practice for CFS or how we may increase the moderate efficacy of these interventions. A straightforward way to search for an answer to these questions is to test which variables mediate the effect of treatment (Baron & Kenny, 1986; Frazier et al., 2004). A significant mediation effect indicates that a treatment works through a change in the intervening variable. In addition, moderators and predictors of the treatment effect can be examined to determine which variables may impede or facilitate the proposed mechanisms of change (Frazier et al., 2004).

Mechanisms of change

Moss-Morris et al. (2005) conducted the first mediation analysis in the context of GET for CFS. This study acted as a model for our analyses of three previously conducted randomised controlled trials (RCTs) of CBT for CFS (chapters 2-4). All analyses showed that a reduction in fatigue could not be explained by a change in physical parameters or physical activity, neither in GET (Moss-Morris et al., 2005) nor in CBT for CFS (Wiborg et al., 2010a). We found no change in the level of physical activity due to our interventions. Nevertheless, all interventions were effective in reducing fatigue and impairment. In sum, these findings do not

support the idea that patients need to reverse physical deconditioning in order to improve (Fulcher & White, 1997).

Instead, all mediation analyses revealed that a persistent change in cognitive processes mediated the effect of treatment. A decrease in focusing on fatigue mediated the effect of GET for CFS (Moss-Morris et al., 2005) and CBT for CFS (Wiborg et al., 2011). A decrease in perceived problems with activity and an increase in perceived control over fatigue were also significant mediators of the effect of CBT for CFS. These two mediators were validated in the same treatment model showing that they added independently of one another to the effect of treatment (Wiborg et al., 2012). A decrease in focusing on symptoms did not yield significance in these latter analyses which may have been due to the instrument that was used to assess focusing on symptoms in the corresponding trial.

Change in physical activity

Mediation analysis helped to elucidate that there is no empirical support for a vital role of changes in physical activity in evidence-based practice for CFS even though this was one of the central ideas of these interventions. It also helped to identify more promising mechanisms based on current insights about the perpetuation of CFS (Knoop et al., 2010a). The validity of these findings might be limited, however, by the fact that in none of the studies mediators were assessed during treatment. A temporary change in physical activity may thus have occurred during treatment which could have facilitated a persistent change in cognitions that might not have been realised otherwise. In that case, temporary changes in physical activity could still be necessary to treat CFS effectively, even though a persistent change in physical activity is not vital to improvement.

The role of physical activity may, however, also vary depending on the activity pattern of patients (van der Werf et al., 2000). Due to the dominance of relatively active patients in our samples, we were not able to test our mediation hypothesis as being moderated by activity pattern. That is, an increase in physical activity may mediate the effect of treatment on the symptomatology of pervasively passive patients but not of relatively active patients. If this was the case, a reversion of physical deconditioning might be a crucial mechanism of change in some but not all patients due to the heterogeneity of the patient population. Analogous to our findings, Bazelmans et al. (2001) found that physical deconditioning is no perpetuating

factor in CFS but suggested to replicate their findings in pervasively passive patients to further validate this conclusion. Changes in physical activity could thus play a role in the treatment of CFS but based on the present findings this role should be limited to temporary influences or subgroups of patients. For the majority of CFS patients, a change in cognitive processes seems to be vital to improvement.

Change in perception

Based on our findings, one important aspect of these cognitive processes concerns a change in perceptual biases with respect to activity. It has been reported before that CFS patients tend to underrate their ability to engage in activity independent of their objective performance (Knoop et al., 2010a). They also tend to stop earlier with physical activities due to a greater perceived effort than matched controls (Fulcher & White, 2000; Bazelmans et al., 2001). We found that a change in perceptual biases mediated the effect of CBT for CFS. In particular, those patients improved who reported a decrease in perceived problems with activity together with an increase in perceived control over fatigue.

Closely related to these mediators is the concept of self-efficacy. With respect to activity in CFS patients, self-efficacy could be defined as the perceived ability to engage in activity despite symptoms. Although we did not directly assess this concept in our studies, our findings may suggest that a successfully accomplished activity program which is not attributed to an increased ability to engage in activity could be one of the reasons why patients do not improve. Therapists may therefore stimulate this attribution by explicitly asking patients whether they are experiencing an increase in their ability to engage in activity during the activity programs. If patients are still reporting a lack of self-efficacy at the end of these programs, therapists might directly intervene by asking what is missing in terms of activity in order to convince the patient that his or her ability to engage in activity has increased since the beginning of the therapy (Knoop & Bleijenberg, 2010b).

In addition, therapists may also consider to discuss with their patients that there is increasing evidence that perceptual biases are a central feature of CFS. They could explain that this means that it is hard for patients to estimate their ability to engage in activity properly. As a consequence, patients tend to invalidate themselves unintentionally. A purpose of the treatment is to learn through activity programs that one is able to engage in meaningful

patterns of activity independent of the symptoms. Bringing these processes to the attention of the patient may help to avoid that changes in activity patterns are misattributed. Also, therapists may be withheld from misinterpreting the role of changes in physical activity as aim in itself and are stimulated to focus on perceptual changes instead.

Change in emotion

Besides cognitive and behavioural processes, emotions may also play a role in CBT for CFS. Godfrey et al. (2007) conducted a study about CBT versus non-directive counselling in primary care patients with fatigue. They gathered ratings on various therapy features based on audio tapes and linked these ratings to treatment outcome. Higher scores on acknowledgement and acceptance of emotional distress during both treatments were associated with less fatigue at six months follow-up. In addition, Brooks et al. (2011) examined change patterns in CBT for CFS and found that more acceptance of fatigue following treatment was associated with less fatigue and better physical functioning. Learning to accept emotional distress and fatigue may thus be an additional mediator of the positive effect of treatment in CFS patients.

It has been proposed that a decrease in fear of activity and related avoidance behaviours may also play a role in the treatment of CFS (Deale et al., 1997; White et al., 2011). Even though we found no evidence for the idea that a decrease in avoidance of activity or aversive stimuli may mediate the effect of CBT for CFS, Deale et al. (1998) found a link between changes in avoidance related beliefs and treatment outcome in CFS patients. In particular, the fear avoidance model may account for the group of pervasively passive patients who disengage from activity without the characteristic bursts of activity which are typically found in relatively active patients. Catastrophising beliefs about the potential harm of activity may feed fear and avoidance of activity in pervasively passive patients. Exposure to activity may help to challenge these beliefs and thereby facilitate a decrease in fear and avoidance of activity which may contribute to the effect of treatment in these patients.

Determinants of the treatment response

Most studies about the response of patients to evidence-based interventions for CFS have focused on the identification of baseline patient characteristics to predict treatment outcome

(Rimes & Chalder, 2005; Prins et al., 2006). A baseline patient characteristic that has been shown to impede treatment outcome may lead to changes in the treatment routine to enhance the efficacy of the intervention. For example, when our research group had found that pervasively passive activity patterns at baseline assessment predicted unfavourable treatment outcomes in CBT for CFS (Prins et al., 2001), we modified our treatment manual which resulted in better outcomes for these patients (Stulemeijer et al., 2005).

Bronwyn et al. (2011) identified the first determinant of the treatment response that exceeded the level of the patient. They found that primary care settings generate significantly smaller effects than secondary care settings, making it disputable whether CBT for CFS should be delivered in primary care. This finding is particularly interesting because it suggests that the range of factors that may impede or facilitate mechanisms of change in the treatment of CFS is not limited to characteristics of the patient. A number of additional variables can be imagined at the level of the therapist and the setting where treatment is delivered which could help to better understand the accomplishment of treatment effects in evidence-based practice for CFS. Taking the interdependence of factors from different levels into consideration may also help to better reflect the complexity of the treatment reality. Such an enhanced understanding could lead to further modifications in the delivery of treatment which may help to enhance the effects of these interventions as well.

In chapter 6, we examined data from three Dutch community-based mental health care centres (MHCs) which implemented or sustained CBT for CFS. Keeping in mind that determinants of the treatment response may exceed the level of the patient, we were particularly interested in the influence of the therapist on treatment outcome. Cella et al. (2011) recently found no therapist effect in a specialised treatment unit for CFS and argued that this finding might be explained by the fact that therapists received the same training in manualised CBT for CFS. If this assumption would hold true outside the context of specialised (academic) treatment settings, a vital source of potential *noise* for successful disseminations of manualised CBT for CFS might be easily controlled for by training.

Yet, Addis & Krasnow (2000) showed that therapists of specialised treatment units are generally positive about manualised therapy which was not necessarily the case outside such settings. Based on these findings, we hypothesised that therapists who work in MHCs may affect treatment outcome and that less favourable beliefs about treatment manuals may predict

less effective therapies. Our analyses confirmed these hypotheses. A substantial part of the treatment effect could be explained by the therapist. The belief of therapists that treatment manuals threaten their freedom and flexibility predicted less favourable treatment outcomes.

At the same time, our findings underscored the need to consider the complexity of the treatment context. When we tested the same baseline model but this time with treatment setting instead of therapists' beliefs as additional factor, we found that the treatment setting explained the therapist effect equally well in our sample. Less favourable beliefs about treatment manuals and higher post-treatment fatigue levels were in fact largely consistent with the setting where treatment was delivered. In particular one MHC, in which a stepped care variant of CBT for CFS was implemented, had the least favourable attitudes towards treatment manuals and the lowest treatment effects of manualised CBT for CFS.

This finding may tell us that therapists with less positive attitudes towards treatment manuals tend to work in settings that tolerate or facilitate these attitudes. If this was the case, MHCs with therapists who largely hold unfavourable attitudes towards treatment manuals should receive additional attention in the dissemination of evidence-based practice for CFS to avoid suppression of established therapy effects. However, due to the small sample size of MHCs we cannot preclude that our findings may also be a consequence of the implementation scenario in which the attitude of the therapist does not play a vital role. Either way, our findings suggest that the context in which patients receive treatment seems to play a role in the accomplishment of therapy effects. The role of contextual factors that may impede central mechanisms of successful change may thereby be generally more important outside specialised treatment settings due to a greater heterogeneity of these settings.

IMPLEMENTING EVIDENCE-BASED PRACTICE FOR CFS

Numerous studies have highlighted the complexity of implementing evidence-based care into clinical practice (e.g. Kitson et al., 1998; Grol & Grimshaw, 1999; Greenhalgh et al., 2004; Cheater et al., 2005; Hemmelgarn et al., 2006, McHugh & Barlow, 2010). Successful implementation thereby depends on various factors which may be categorised into the nature of the evidence itself, the strategy which is used to facilitate the implementation process, and the context in which the intervention is implemented (Kitson et al., 1998).

Evidence

There is by now extensive support from RCTs that CBT for CFS is an efficacious treatment for patients with CFS. The review by Bronwyn (2011) estimated that about 150 clinical trials with null results would be required to reduce the current effect size of CBT for CFS to a level that is no longer significant. Less is known about the effectiveness of CBT for CFS in clinical practice. The only two studies that reported about the effects of CBT for CFS outside the context of RCTs were conducted by Quarmby et al. (2007) and Scheeres et al. (2008a).

Quarmby et al. (2007) compared treatment effects within and without the scope of a RCT in the same treatment unit. They found less favourable effect sizes outside the scope of their RCT and therefore concluded that CBT is less effective in clinical practice. It has been criticised, however, that only one experienced therapist treated all patients in the RCT condition which may have led to an inflation of the treatment effects in this condition (Scheeres et al., 2008a). Scheeres et al. (2008a) conducted a study in which CBT for CFS was implemented by a Dutch MHC and compared their findings with the results of four RCTs in which CBT for CFS was delivered. Their benchmark approach resulted in treatment effects of the MHC that were similar to those of RCTs. Consistently, they concluded that CBT for CFS does not have to be less effective in clinical practice and that MHCs seem to be suitable to deliver this treatment effectively.

Strategy

Scheeres et al. (2008a) paid particular attention to the conditions under which CBT for CFS can be implemented successfully outside specialised treatment units. Based on the recommendations of Grol et al. (1999), they conducted an analysis of potential barriers prior to the actual implementation process and designed interventions to overcome these barriers. The main problems that were anticipated were inexperience of therapists with the management of somatic complaints and a lack of awareness among referrers and patients about the new treatment. Their interventions included the training and supervision of therapists and regular activities to inform referrers and patients about CBT for CFS. Based on their experiences of the actual implementation process, they extended their list of conditions for successful implementation of CBT for CFS in MHCs. In particular, they added the aspect of starting treatments within a narrow time frame to avoid unexpectedly high drop-out rates.

These preconditions were discussed in an implementation manual which was designed to facilitate future implementations of CBT for CFS in MHCs independent of external support agents (Scheeres et al., 2006).

In chapter 5, we explored whether MHCs are able to independently implement and sustain CBT for CFS based on the implementation manual. We monitored the implementation process of three Dutch MHCs for this purpose. One sustained CBT for CFS from the implementation study of Scheeres et al. (2008a). Two MHCs newly implemented CBT for CFS, one in the context of a stepped care program. We delivered the training and supervision for new therapists based on our treatment manual (Bleijenberg et al., 2003; Knoop et al., 2010b) and introduced the implementation manual (Scheeres et al., 2006) to their team leaders. During the implementation process, substantial problems were detected based on our monitoring data so that external support in addition to the implementation manual was delivered to the two MHCs which newly implemented CBT for CFS. Ultimately, all MHCs reached the predefined implementation success criteria in terms of numbers of included patients and post-treatment assessments. A benchmark analysis revealed that overall treatment effect sizes were similar to those of RCTs, except for the MHC where a stepped care program for CFS was implemented.

Our support for the two new MHCs was based on the work of Scheeres et al. (2006; 2008a). The main part of our assistance included a translation of the standardised implementation manual of Scheeres et al. (2006) into practice based on regular feedback for team leaders about the performance of their MHC. In addition, we searched for further implementation problems and suggested solutions based on the specific needs of the MHCs (Grol et al., 1999, Cheater et al., 2005; Bosch et al., 2007). For example, treatment periods were often unexpectedly long which delayed the start of new treatments and increased the risk for drop-out. We therefore stimulated the administrative employees of the two MHCs to remind therapists of treatments which exceeded the recommended time frame of six months. We sought to empower team leaders during this process by communicating *at eye level* (Greenhalgh et al., 2004), leaving it to them to determine how much concrete support was delivered in addition to the regular feedback. According to the team leaders, both MHCs benefited from this assistance.

Although we expected that MHCs would be able to implement CBT for CFS without additional support, we experienced our assistance as substantially less intensive than that of the study by Scheeres et al. (2008a) where no implementation manual existed. Thus, even though the implementation manual does not seem to substitute additional support by external experts, it seems to help make the support more efficient. Our data further suggest that MHCs are able to sustain CBT for CFS independently after the initial implementation period. In general, there seem to be parallels between the need of therapists for supervision to deliver a new treatment approach based on a treatment manual and the need of team leaders for supervision to implement a new treatment approach based on an implementation manual (Fixsen et al., 2009). We obviously underestimated the latter need when we started with our implementation study.

Context

In chapter 6, we found that less favourable attitudes of therapists towards the use of treatment manuals predicted less effective treatments. In line with this finding, the utilisation of evidence-based practice by mental health care providers has generally been found to be associated with positive attitudes towards the evidence-based standard (Stahmer & Aarons, 2009). However, in our sample, the setting where treatment was delivered was also a possible explanation for the variation in therapist efficacy. Less favourable attitudes and less effective treatments were actually augmented within the same treatment setting (i.e. the setting where stepped care for CFS was implemented). Besides the specific implementation scenario, other characteristics of the treatment setting, such as the organisational culture and climate towards evidence-based practice (Hemmelgarn et al., 2006; Aarons & Sawitzky, 2006), may affect successful dissemination of evidence-based practice for CFS. These characteristics may interact with characteristics of the therapists that deliver treatment at these settings.

Stepped care

Even though regular CBT for CFS was less effective in the MHC with the stepped care approach, the results of the minimal intervention were promising at this MHC. Recovery rates outranged those of a waiting list control group and were similar to those found in our specialised treatment unit (Knoop et al., 2008). Yet, due to the less favourable treatment effect

sizes in the regular CBT condition, implementation of the minimal intervention can better be postponed until cognitive behavioural therapists have had sufficient time to develop a certain routine in delivering regular CBT for CFS.

As additional part of the stepped care approach, patients who do not recover from CFS after regular CBT may be referred to specialised tertiary care settings. In our implementation study, additional treatment in such a specialised setting was an option for all patients who did not respond to treatment in one of the MHCs. However, few patients were actually referred. Interestingly, a considerable number of non-responders were not even asked by their therapists whether or not they would appreciate specialised care, even though it was agreed upon by all professionals that every patient who did not recover according to our criteria would be offered a referral to tertiary care as a standard procedure. When patients were referred to a specialised setting in the context of our study, they often benefited from that intervention. However, the number of patients was small and there may be a selection bias as therapists may be more likely to refer patients of whom they think that additional treatment might work.

POTENTIAL LIMITS OF EVIDENCE-BASED PRACTICE FOR CFS

In chapter 7, we examined illness-specific characteristics of homebound patients and found that these patients differ considerably from patients who usually participate in treatment studies (Wiborg et al., 2010b). Homebound patients were characterised by extreme scores on daily fatigue and functional impairment, a predominant somatic attribution, and extremely passive activity patterns. Particularly striking to us was the fact that these extreme scores were stable across time while none accepted our offer to receive treatment.

Our data suggest that these patients may have accepted the fact that there is no suitable treatment for them. In particular, we found that the scores on psychological distress and loss of control were not inflated despite their extreme scores on physical complaints and functional impairment. Due to their predominant somatic attributions, these patients may also find any treatment unacceptable which is not strictly somatic in nature. The lack of motivation in these patients to follow a cognitive behavioural intervention might thereby be understood as a very powerful determinant of the treatment response at a pre-treatment level.

The clinical guidelines for the management of CFS of the National Institute for Health and Clinical Excellence in the UK suggest to motivate patients with such severe CFS by explaining the associated health risks of their current behaviour to them (Turnbull et al., 2007; pp. 36-37). This explanation should be accompanied with the offer of individually tailored activity management programs based on the principles of CBT and GET for CFS which can be delivered at home or by telephone and internet. Future studies will have to show how effective such motivational interventions are and whether previous findings about evidence-based practice for CFS will generalise to this group of patients.

At the same time, preventive actions might be considered to help avoid the extreme illness patterns found in homebound patients. Most importantly, the rigidity of somatic attributions might be prevented by health care professionals who offer an explanatory model for the symptoms that encompasses an interplay of biological, psychological and social factors early in the development of CFS. Such a model has been shown to positively affect the responsiveness of patients with medically unexplained symptoms towards psychotherapeutic interventions and their prognosis to profit from these interventions (Dowrick et al., 2004).

A lack of knowledge and scepticism towards the diagnosis and treatment of CFS at the level of the health care professional may interfere with such a balanced approach in the disadvantage of the patient who is withheld from evidence-based practice (Wiborg et al., 2008). Written informational interventions may help to inform professionals about the state of the art in the management of CFS and increase referrals to evidence-based interventions (Scheeres et al., 2007).

FUTURE DIRECTIONS

Research about mechanisms of change and determinants of the treatment response

Although our mediation analyses generated valuable insights about how CBT for CFS may work, our findings clearly need to be validated by replication. The role of changes in perceptual and attentional biases could thereby be examined in all variants of evidence-based practice for CFS to determine whether these changes are general features of successful treatment for CFS. Prospective studies which are specifically designed to measure treatment process will help to determine causality among the factors of our model and help to shed light

to the role of temporary changes in physical activity in the treatment of CFS. Future studies should also examine the hypothesis of moderated mediation in pervasively passive patients.

A maximum of three-quarter of the effect of treatment on fatigue and physical functioning was accounted for by the mediators of our treatment model. In case of overall impairment, only about half of the effect of treatment was explained by our mediators. The introduction of focusing on fatigue to our model, assessed as in the studies by Moss-Morris et al. (2005) or Wiborg et al. (2011), may substantially enhance the overall mediation effect. However, other factors may also contribute to our model. Promising candidates are self-efficacy with respect to activity as well as acceptance of emotional distress and fatigue (Godfrey et al., 2007; Brooks et al., 2011). In case of overall impairment, balanced levels of social support may substantially contribute to the mediation effect as well (Prins et al., 2004). More research on the determinants of unfavourable treatment responses in community-based settings is needed to better understand which variables may threaten established therapy effects outside specialised treatment settings. Among other things, the exact role of the attitude of therapists towards treatment manuals (Addis et al., 2000) as well as specific characteristics of the treatment setting, such as the organisational climate and culture towards evidence-based practice (Hemmelgarn et al., 2006; Aarons & Sawitzky, 2006), should be further examined. Specific interventions could be developed and tested based on these new insights to positively influence unfavourable characteristics of the dissemination context whenever possible.

National implementation of stepped care

An estimated minimum of 30.000 to 40.000 people suffer from CFS in the Netherlands (Gezondheidsraad, 2005). Treatment settings for the delivery of evidence-based interventions for CFS are scarce so that many of these people do not receive adequate treatment. Based on the available findings, the implementation of stepped care for CFS on a national scale is feasible and cost-effective for MHCs after a period of initial investment (Tummers et al., 2011; van Dam et al., 2011). Implementing CBT for CFS is also cost-effective from a societal perspective by helping to cut the immense health costs of these patients (McCrone et al., 2004; Severens et al., 2004; Scheeres et al., 2008b). State grants which are designed to tackle

problems with the initial investment may help to stimulate MHCs to implement stepped care for CFS.

The general pursuit of national implementation of stepped care for CFS is to facilitate early intervention based on the evidence-based standard in the region of the patient. Treatment effects should thereby be continuously monitored by MHCs to warrant high quality of care. According to our experience, CFS therapists should have followed the basic training for cognitive behaviour therapy of the Dutch association for behavioural and cognitive therapy (VGCT) as a minimum. After training in CBT for CFS, therapists should have the possibility to treat at least six, preferably more, CFS patients per year to develop a routine in the treatment of these patients. Our centre has initiated an accreditation of CFS therapists which may serve as a guide for adequate quality of care. In the context of a *train the trainers* program, therapists can also learn to train and supervise colleagues which can help to further cut costs for MHCs.

Concerning the implementation process, we suggest that new implementations of evidence-based practice for CFS are accompanied by external experts during a period of two to three years depending on the implementation scenario and the needs of the individual MHC. This assistance can be based on the implementation manual of Scheeres et al. (2006) and includes regular feedback on the treatment process and outcome data. In the context of stepped care, we suggest that cognitive behavioural therapists get the opportunity to develop a routine in the delivery of regular CBT first. About one to two years of practice should be appropriate depending on the outcomes of the individual treatment setting. Special training for cognitive behavioural therapists in treating patients who did not recover after the minimal intervention may be offered in addition to avoid suppression of established therapy effects.

In the context of stepped care for CFS, empirically supported selection criteria are needed to determine which patients should receive the low intensity intervention and which patients could better directly start with regular CBT for CFS. Some patients may also need to be referred directly to specialised tertiary care settings. There are already data which suggest that the minimal intervention is not suitable for patients with very severe disabilities (Knoop et al., 2008). With evidence-based selection criteria, one single tailored treatment might suffice to facilitate substantial improvement which would make stepped care more efficient and effective by minimising the chance of non-response (Bower et al., 2005). Finally, the

readiness of MHC therapists to refer patients to tertiary care settings might be increased by demonstrating that these settings are effective in treating complex patients who did not yet recover.

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Summary

According to the consensus criteria of the US Centre for Disease Control, chronic fatigue syndrome (CFS) is characterised by severe fatigue which lasts for at least six months. Additional complaints such as pain, concentration problems and unrefreshing sleep are frequently reported. These complaints are not the result of a medical condition and lead to substantial impairment. Cognitive behaviour therapy (CBT) is an evidence-based intervention for patients with CFS. Despite the available evidence for the efficacy of cognitive behavioural interventions for CFS, little is known about the mechanisms of change that are at work in these interventions. In this thesis, we tested some of the most influential models about how these interventions might generate their effects. In addition, we were interested in how CBT for CFS can be successfully implemented outside specialised treatment settings. In *chapter 1*, a detailed introduction to the topic was presented together with the outline of the thesis.

Physical activity programs are a common way to treat patients with CFS. In these programs, the level of physical activities is gradually increased. Consistently, the idea that an increase in physical activity could be responsible for the improvement of CFS patients is widely held. In *chapter 2*, we tested whether the effect of CBT on fatigue severity is mediated by a persistent increase in physical activity. For this purpose, we reanalysed three randomised controlled trials (RCTs) that were previously conducted in the context of CBT for CFS. In all samples, actigraphy was used to assess the level of physical activity prior and subsequent to a treatment or control group period. Although CBT reduced fatigue, it did not change the level of physical activity. Changes in physical activity were also not related to changes in fatigue. Across the samples, we found a mean mediation effect of physical activity of about 1% of the total treatment effect which did not yield significance. We therefore concluded that the effect of CBT on fatigue in CFS is not mediated by a persistent increase in physical activity.

In *chapter 3*, we examined whether CBT for CFS works because it affects maladaptive coping strategies. We were interested in whether the effect of CBT for CFS on fatigue and impairment is mediated by a decrease in avoidance behaviour and focusing on fatigue. The role of these strategies in the perpetuation of symptoms has been stressed by the cognitive behavioural model for CFS. We reanalysed the largest of our RCTs for this purpose in which a coping questionnaire was used to assess how patients react to their fatigue. Mediation

analysis revealed that a decrease in focusing on fatigue mediated the effect of CBT for CFS on fatigue and impairment. Neither avoidance of activity nor avoidance of aversive stimuli were significantly changed by treatment and were therefore excluded from mediation analysis. We concluded that a decrease in the focus on fatigue contributes to the treatment effect of CBT for CFS.

Based on the findings of chapters 2 and 3, we developed and tested a treatment model for cognitive behavioural interventions focusing on CFS in *chapter 4*. We were interested in whether CBT for CFS might work because it leads to a persistent change in cognitive processes. These processes include (1) a decrease in focusing on symptoms, (2) a decrease in perceived problems with activity and (3) an increase in sense of control over fatigue. We hypothesised that these changes might mediate the effect of our intervention on fatigue severity and disabilities. We tested these hypotheses in the most recent of our RCTs in which a low intensity variant of CBT for CFS was compared to a waiting list control group. Structural equation modelling resulted in a model in which the effect of treatment was mediated by a decrease in perceived problems with activity and an increase in sense of control over fatigue. We concluded that cognitive behavioural interventions for CFS need to change the illness perception and beliefs of their patients in order to be effective.

In *chapter 5*, we presented the monitoring data of three Dutch community-based mental health care centres (MHCs) which implemented or sustained CBT for CFS based on an implementation manual. In contrast to what we expected, the two MHCs that implemented CBT for CFS needed assistance in addition to the implementation manual. This support was delivered during the second half of the implementation process. All settings ultimately reached the predefined criteria for successful implementation with overall treatment effect sizes being similar to those found in RCTs. Only one MHC, which implemented CBT simultaneously with a low intensity intervention in the context of stepped care for CFS, produced significantly lower effect sizes in the regular CBT condition. These findings suggest that external support in addition to an implementation manual is needed to help coordinate the initial implementation of CBT for CFS. After initial implementation, MHCs seem able to sustain CBT for CFS successfully without additional support. The treatment effect sizes were

promising with respect to large-scale dissemination of CBT for CFS outside specialised treatment settings. Successive implementation of cognitive behavioural interventions for CFS should be considered in the context of stepped care for CFS.

In *chapter 6*, we used the routinely collected outcome data of the three MHCs to explore the role of the therapist in the dissemination of manualised CBT for CFS outside specialised treatment settings. Ten therapists, who all received the same training in CBT for CFS, and 103 patients with CFS were included. Random effects modelling revealed a significant difference in mean post-treatment fatigue between therapists. This effect could be explained by the therapists' attitude towards working with evidence-based treatment manuals. However, we found that the treatment setting where patients received CBT for CFS could explain the findings equally well. We therefore concluded that the context in which patients receive CBT for CFS may play an important role in the accomplishment of established therapy effects outside specialised treatment settings.

A substantial number of CFS patients seem to experience periods in which they are bound to home due to their symptomatology. Despite the ever growing body of knowledge about CFS, little is known about patients who feel no longer able to leave their house. In *chapter 7*, we compared the characteristics of these patients with those of other CFS patients who participated in the natural course condition of a RCT. Besides experiencing more impairment in daily functioning than the participants of the RCT, homebound patients were characterised by extremely high levels of daily fatigue, predominant somatic attributions and pervasively passive activity patterns. The course of symptomatology was stable in both groups. We concluded that homebound patients seem to form a distinct subgroup of CFS patients.

In *chapter 8*, the findings of the previous chapters were discussed in more detail. At first, mechanisms of change and determinants of the treatment response of evidence-based interventions for CFS were discussed. Based on our findings, a persistent change in cognitive processes seems to be central to CBT for CFS. The context in which CFS patients receive treatment may thereby affect therapy outcomes. A focus on central change processes and modifications in the design and delivery of CBT for CFS in reaction to poor responses may

help to enhance the generally moderate efficacy of treatment. Next, we discussed the dissemination of CBT for CFS in MHCs, including strategies which may help to facilitate implementation success. We also commented on potential limits of evidence-based practice for CFS based on our findings about homebound patients. Finally, we discussed directions for future research and made suggestions for national implementation of stepped care for CFS.

Samenvatting

Volgens de consensus criteria van het US Centre for Disease Control wordt het chronisch vermoeidheidssyndroom (CVS) gekenmerkt door ernstige vermoeidheid die tenminste zes maanden voortduurt. Er worden vaak ook additionele klachten, zoals pijn of concentratie- en slaapproblemen, gerapporteerd. Deze klachten zijn niet het gevolg van een somatische aandoening en zorgen voor aanzienlijke beperkingen in het dagelijks functioneren. Cognitieve gedragstherapie (CGT) is een bewezen werkzame behandeling voor patiënten met CVS. Hoewel er veel onderzoek naar de effectiviteit van CGT voor CVS is gedaan, is er nog weinig bekend over de mechanismen die het effect van de behandeling bewerkstelligen. In dit proefschrift werden sommige van de meest invloedrijke modellen getest over hoe deze behandelingen zouden kunnen werken. Daarnaast waren wij geïnteresseerd in de vraag hoe CGT voor CVS het beste in de praktijk geïmplementeerd zou kunnen worden. In *hoofdstuk 1* werden achtergrond en vraagstellingen van dit proefschrift geïntroduceerd.

Lichamelijke activiteiten programma's zijn een gebruikelijke manier om patiënten met CVS te behandelen. In deze programma's wordt het niveau van lichamelijke activiteit stapsgewijs uitgebreid. Het idee is dat een toename van lichamelijke activiteit helpt om minder moe te worden. In *hoofdstuk 2* werd de hypothese getoetst dat een toename van lichamelijke activiteit het effect van CGT voor CVS medieert. Daarvoor werden drie gerandomiseerde en gecontroleerde trials (RCTs), waarin de effectiviteit van CGT voor CVS werd getoetst, opnieuw geanalyseerd. In alle steekproeven werd Actigrafie gebruikt om lichamelijke activiteit voor en na de behandeling of controle conditie te meten. Alhoewel de behandeling leidde tot een afname van vermoeidheid, veranderde de behandeling het niveau van lichamelijke activiteit niet. Veranderingen in lichamelijke activiteit en vermoeidheid waren bovendien niet gerelateerd aan elkaar. Het effect van de behandeling dat door een toename van lichamelijke activiteit gemedieerd werd lag bij ongeveer 1 procent en was in geen van de studies significant. We concludeerden daarom dat het positieve effect van CGT op vermoeidheid bij CVS niet door een blijvende toename in fysieke activiteit gemedieerd wordt.

In *hoofdstuk 3* werd de hypothese getoetst dat de vermoeidheid in CGT voor CVS afneemt omdat dysfunctionele coping strategieën worden veranderd. Getoetst werd of het effect van CGT voor CVS op vermoeidheid en beperkingen gemedieerd werd door een afname in

vermijdingsgedrag en een afname in de gerichtheid op vermoeidheid. Beide coping strategieën hebben een prominente plaats in het cognitief-gedragsmatig model voor CVS. We analyseerden de grootste van onze drie trials waarin een coping vragenlijst werd afgenomen om patiënten te vragen hoe zij met vermoeidheid omgaan. De mediatieanalyse liet zien dat een afname in de gerichtheid op vermoeidheid het effect van CGT voor CVS op vermoeidheid en beperkingen medieerde. De vermijding van activiteit en aversieve stimuli werd daarentegen niet door de behandeling veranderd en werd daarom geëxcludeerd van een verdere mediatie analyse. We concludeerden dat een afname in de gerichtheid op vermoeidheid een bijdrage levert aan het effect van CGT voor CVS.

Gebaseerd op de bevindingen in hoofdstuk 2 en 3, werd in *hoofdstuk 4* een model voor de behandeling van patiënten met CGT voor CVS ontwikkeld en getoetst. De vraag was of CGT voor CVS werkt via een blijvende verandering in cognitieve processen. Deze processen betreffen (1) een afname in de gerichtheid op vermoeidheid (2) een afname in ervaren problemen met activiteit en (3) een toename in ervaren controle over de klachten. Verondersteld werd dat deze veranderingen het effect van onze interventie op vermoeidheid en beperkingen zou mediëren. Deze hypothesen werden in onze meest recente trial getoetst waarin een minimale variant van CGT voor CVS vergeleken werd met een wachtlijst controle conditie. Structural equation modelling leverde een model op waarin een afname in ervaren problemen met activiteit en een toename in ervaren controle over de vermoeidheid het effect van de behandeling medieerde. We concludeerden dat CGT voor CVS de waarneming van en gedachten over de aandoening moet veranderen om effectief te zijn.

In *hoofdstuk 5* presenteerden wij gegevens van drie Nederlandse GGZ instellingen waarvan twee CGT voor CVS op basis van een implementatie handleiding implementeerden en één GGZ instelling een eerdere implementatie voortzette. In tegenstelling tot wat wij hadden verwacht was er bij de twee nieuwe instellingen extra ondersteuning nodig naast de implementatie handleiding. Deze ondersteuning werd tijdens de tweede helft van het implementatieproces geleverd. Alle GGZ instellingen hebben uiteindelijk de van tevoren vastgestelde criteria voor succesvolle implementatie behaald. De effectiviteit van de uitgevoerde behandelingen was daarbij vergelijkbaar met die van RCTs. Slechts één GGZ

instelling, waar reguliere CGT gelijktijdig met een minimale interventie voor CVS werd geïmplementeerd in het kader van getrapte zorg, liet minder goede resultaten zien bij reguliere CGT. Deze bevindingen laten zien dat GGZ instellingen in de eerste periode van de implementatie van CGT voor CVS ondersteuning van externe deskundigen nodig hebben, wil de implementatie slagen. Daarna lijken deze instellingen in staat de geïmplementeerde behandeling op eigen kracht zonder verdere ondersteuning voort te kunnen zetten. De resultaten uit deze studie zijn veelbelovend met het oog op landelijke implementatie van CGT voor CVS. Op basis van de geringere resultaten van reguliere CGT in geval van implementatie van getrapte zorg, werd voorgesteld eerst reguliere CGT voor CVS te implementeren en pas later de minimale interventie.

In *hoofdstuk 6* hebben we de gegevens van de drie GGZ instellingen verder geanalyseerd om de rol van therapeuten bij de implementatie van CGT voor CVS buiten specialistische behandelcentra te onderzoeken. Tien therapeuten die allemaal dezelfde training in CGT voor CVS hadden gevolgd en 103 patiënten met CVS werden geïncludeerd. Random effects modelling liet zien dat er significante verschillen in effecten waren tussen de therapeuten. Deze verschillen konden door de houding van therapeuten ten opzichte van protocollair werken worden verklaard. De verschillen waren echter ook te verklaren door de instelling waar CGT voor CVS aangeboden werd. We concludeerden daarom dat de context waarin patiënten voor CVS behandeld worden, zou kunnen verklaren waarom behandeleffecten buiten specialistische centra verschillen.

Een substantieel aantal CVS patiënten lijkt perioden te kennen waarin zij door hun klachten aan huis of bed gebonden zijn. Er zijn echter nauwelijks data beschikbaar over patiënten die zich niet in staat voelen huis of bed te verlaten. In *hoofdstuk 7* hebben we de kenmerken van deze patiënten vergeleken met die van andere CVS patiënten die in de natuurlijk beloop conditie van een RCT zaten. De patiënten die aangaven niet in staat te zijn huis of bed te verlaten waren niet alleen meer beperkt in hun dagelijks functioneren. Deze patiënten hadden ook meer extreme dagelijkse vermoeidheid, sterkere somatische attributies en waren lichamelijk duidelijk minder actief dan de patiënten uit de RCT. Het verloop van de klachten

was stabiel in beide groepen. We concludeerden dat patiënten die aangeven huis of bed niet te kunnen verlaten een aparte subgroep van CVS patiënten vormen.

In *hoofdstuk 8* werden de resultaten uit de eerdere hoofdstukken besproken. Als eerste werden de veranderingsmechanismen en determinanten van de behandelrespons bij bewezen werkzame behandelingen voor CVS besproken. Op basis van onze bevindingen lijkt een blijvende verandering in cognitieve processen een centrale rol in de behandeling van CVS te spelen. Tevens lijkt de context waarin patiënten behandeling ontvangen de behandelresultaten te beïnvloeden. Meer aandacht voor de verandering van deze cognitieve processen en de manier waarop CGT voor CVS wordt aangeboden zou de effecten van de behandeling verder kunnen verbeteren. Vervolgens werd de verspreiding van CGT voor CVS in de GGZ besproken en werden suggesties gedaan welke implementatiestrategieën hierbij kunnen helpen. We bespraken bovendien mogelijke grenzen van bewezen werkzame behandelingen voor CVS op basis van onze bevindingen over patiënten die aan bed of huis zijn gebonden. Tot slot werden aanbevelingen voor toekomstig onderzoek en landelijke implementatie van stepped care voor CVS gedaan.

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About the author

Jan-Frederic Wiborg was born 1978 in Husum, Germany. He holds a bachelor of social work and graduated his study of clinical psychology with honours at the Radboud University of Nijmegen, the Netherlands. After his study, he started to work as a junior researcher and therapist at the Expert Centre for Chronic Fatigue of the Radboud University Nijmegen Medical Centre. Currently, he lives with his wife Maria and son Joshua in Hamburg, Germany, where he is working at the Department of Psychosomatic Medicine and Psychotherapy of the University Medical Centre Hamburg-Eppendorf.